Single Technology Appraisal

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Eli Lilly**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation

4. **Evidence Review Group report** prepared by **Liverpool Reviews and Implementation Group**

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Eli Lilly**

7. **Technical engagement responses & expert statements from experts:**
   a. Professor James Spicer, clinical expert nominated by NCRI-ACP-RCP-RCR

8. **Technical engagement response from consultees and commentators:**
   a. Roche

9. **Evidence Review Group critique of company response to technical engagement** prepared by **Liverpool Reviews and Implementation Group**

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 *RET* fusion-positive advanced non-small cell lung cancer [ID3743]

Document B

Company evidence submission

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Abbreviations

Acronym	Definition
ACIC	Academic/commercial in confidence
ACTH	Adrenocorticotropic hormone
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
AUC	Area under curve
BIC	Bayesian information criteria
BID	Twice daily
BNF	British nation formulary
BOR	Best objective response
BSA	Best surface area
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CGDB	Clinico-Genomic database
CHMP	Committee for Medicinal Products for Human Use
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOC	Docetaxel
DOCK	Dedicator of cytokinesis
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EHR	Electronic health record
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FISH	Fluorescence in-situ hybridisation
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
KRAS	Kirsten rat sarcoma
LPS	Lansky Performance Score
LTFU	Lost to follow-up
LYG	Life years gained
MAPK	Mitogen-activated protein kinase
MKI	Multi-kinase inhibitor
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OSAS	Overall Safety Analysis Set
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PCR	Polymerase chain reaction
PEM	Pemetrexed
PFS	Progression free survival
PPI	Proton pump inhibitor
PPS	Post-progression survival
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised control trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RET	Rearranged during transfection
ROS-1	C-ros oncogene 1
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAS	Safety Analysis Set
SCE	Summary of Clinical Efficacy
SFU	Safety follow-up
SLR	Systematic literature review
SRC	Safety Review Committee
STAT	Signal transducer and activator of transcription
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TMLE	Targeted minimum loss-based estimation
TPS	Tumour proportion score
TSD	Technical support document
TTD	Time to treatment discontinuation

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

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 treatment of people with advanced, rearranged during transfection (*RET*) fusion-positive, non-small cell lung cancer (NSCLC) who require systemic therapy. Selpercatinib is intended for use in both first line (treatment naïve) and second line (pre-treated patients who have received one or more prior therapies) patient populations, but is expected to be used in the first line setting (on confirmation of *RET* fusion-positive status) in the majority of cases in consideration of its clinical effectiveness (see Section B.2).

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

Eli Lilly and Company are actively seeking funding from the Cancer Drugs Fund (CDF) for selpercatinib in *RET* fusion-positive NSCLC, given the immaturity of the survival data presented in this submission. This uncertainty will be resolved as further survival data becomes available from LIBRETTO-001.[1] Eli Lilly and Company additionally acknowledge that no direct comparative data are currently available for selpercatinib in *RET* fusion-positive NSCLC, however, direct comparative results for the efficacy of selpercatinib versus an active comparator will be available in first line patients with advanced or metastatic *RET* fusion-positive NSCLC from LIBRETTO-431, an ongoing Phase III trial.[2] Uncertainties around the generalisability of participants included within LIBRETTO-001 to the English context, as well as uncertainties around the prevalence of *RET* fusions in NSCLC, are anticipated to be resolved with further data collection from the NHS England Systemic Anti-Cancer Therapy (SACT) dataset.[3]

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	People with advanced *RET* fusion-positive NSCLC who require systemic therapy	People with advanced, non-squamous, *RET* fusion-positive NSCLC who require systemic therapy	*RET* fusions rarely occur in NSCLC tumours with squamous histology.[4] NSCLC patients participating within LIBRETTO-001 were identified to have non-squamous histology in the overwhelming majority of cases, and consequently the target population has been restricted to mirror this in the submission
Intervention	Selpercatinib	Selpercatinib (160 mg) BID	In line with final NICE scope
Comparator(s)	**Untreated (non-squamous):** For people with **non-squamous** NSCLC whose tumours express programmed death ligand-1 (PD-L1) with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy[a] (subject to NICE appraisal) 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[a] (subject to NICE appraisal)	**First line non-squamous NSCLC:** • Pembrolizumab + pemetrexed + platinum chemotherapy[a,d] (TA557) (all patients) • Pembrolizumab (TA531) (PD-L1≥50%) • Atezolizumab + bevacizumab + carboplatin + paclitaxel (TA584) (PD-L1 TPS<50%) **Second line non-squamous NSCLC:** • Pembrolizumab (TA428) (PD-L1≥1%) • Nivolumab[d] (TA484) (PD-L1≥1%) • Atezolizumab (TA520) (all patients)	The target population has been restricted to patients with non-squamous histology, in line with the population of the LIBRETTO-001 study.[1] As a result, comparators presented in the final scope relevant to the squamous population are not included in the submission[5] In the first line population, Eli Lilly and Company's market share data indicate that immunotherapy is replacing existing chemotherapy in routine clinical practice (see Section B.1.3.2). Consequently, platinum doublet chemotherapy (NG122 or TA181) and pemetrexed + carboplatin/cisplatin (NG122) were not considered to be appropriate comparators to selpercatinib

	• Atezolizumab + bevacizumab + carboplatin + paclitaxel • Chemotherapy[b] + platinum drug[a] ± pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed + platinum drug[a] (± pemetrexed maintenance following cisplatin only) **Previously treated disease (non-squamous):** For people with **non-squamous** NSCLC PD-L1 ≥50%: • Platinum doublet therapy[c] • Pemetrexed + carboplatin • Docetaxel (for adenocarcinoma histology) with or without nintedanib • Best supportive care For people with **non-squamous** NSCLC PD-L1 <50%: • Atezolizumab monotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel (only after failed initial EGFR or ALK targeted treatment) • Pembrolizumab monotherapy	• Docetaxel with nintedanib (TA347) (all patients)	In the second line population, atezolizumab with bevacizumab, carboplatin and paclitaxel has not been included as a comparator. NICE guidance (TA584) recommends this treatment only after failed initial epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) targeted treatment. However, *RET* fusions tend to be mutually exclusive with other major lung cancer oncogenic drivers,[6] and therefore this combination was not considered to be an appropriate comparator to selpercatinib Ely Lilly and Company's market share data also indicate that platinum doublet chemotherapy (e.g. gemcitabine + platinum chemotherapy) (NG122) and pemetrexed + carboplatin (NG122) comprise a small UK market share in the second line setting (see Section B.1.3.2). Declining use of platinum doublet chemotherapy (NG122) and pemetrexed + carboplatin (NG122), due to increasing use of immunotherapies, means that these regimens were not considered to be relevant comparators for second line patients in this submission Based on clinical feedback received by Eli Lilly and Company, docetaxel monotherapy (TA347) was not

	• Nivolumab monotherapy • Docetaxel (for adenocarcinoma histology) with or without nintedanib • Best supportive care **Untreated (squamous):** For people with **squamous** NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (subject to NICE appraisal) 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 (subject to NICE appraisal) **Previously treated disease (squamous):** For people with **squamous** NSCLC PD-L1 >50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin		included as a comparator as combination treatment (docetaxel with nintedanib) is preferentially used in clinical practice

	• Docetaxel • Best supportive care For people with **squamous** NSCLC PD-L1 <50%: • Atezolizumab • Nivolumab • Pembrolizumab • Docetaxel • Best supportive care		
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Response rate • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life (HRQoL)	Primary: • Objective response rate (ORR) Secondary: • Duration of response (DOR) • PFS • OS HRQoL: • European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30) Safety outcomes: • Adverse events (AEs)	In addition to outcomes listed in the final NICE scope, duration of response is also considered as part of this submission Time to treatment discontinuation for selpercatinib was explored as part of the cost-effectiveness analysis (Section B.3.3.3)
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY) • The reference case stipulates that the time horizon for	• 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	• Given the transition to testing by next generation sequencing (NGS) at Genomic Hubs is expected in England during the technology appraisal process, local costs of testing for RET are not included in the economic

	estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an National Health Service (NHS) and Personal Social Services (PSS) perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account • The use of selpercatinib in NSCLC is conditional on the presence of *RET* gene fusion. The economic modelling should include the costs associated with diagnostic testing for *RET* in people with advanced NSCLC cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test	incremental cost per QALY • 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	analysis • [redacted] Therefore, submission results are presented at list price. It was not possible to include discounts for comparators due to confidentiality • With the release of NHS England's new test directory, which includes *RET* NGS testing for NSCLC, the cost of testing for *RET* gene fusion was considered an absorbed cost[7]
Subgroups to be considered	• If evidence allows, a subgroup analysis will be performed by previous therapy	First and second line patient populations	In line with final NICE scope

	• The availability and cost of biosimilar and generic products should be taken into account		
Special considerations including issues related to equity or equality	NA	In the technology appraisal of entrectinib for treating c-ros oncogene 1 (ROS1)-positive advanced NSCLC (TA643), concerns related to inequitable access to targeted treatments, due to regional variation in molecular testing practices, were discussed. In England, the transition to NGS testing, completed at Genomic Hubs, means it will be possible to test for *RET* rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres. As such, this equality consideration is not expected to be a concern in this submission	None

Footnotes: [a]Carboplatin or cisplatin; [b]Docetaxel, gemcitabine, paclitaxel or vinorelbine; [c]Cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel or vinorelbine; [d]NICE appraisal following Cancer Drugs Fund exit.

Abbreviations: AE: adverse events; ALK: anaplastic lymphoma kinase; BID: twice daily; CDF: Cancer Drugs Fund; DOR: duration of response; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; HRQoL: health-related quality of life; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS; overall survival; PAS: Patient Access Scheme; PASLU: Patient Access Scheme Liaison Unit; PD-L1: programmed death-ligand 1; PFS: progression free survival; PSS: personal social services; QALY: quality-adjusted life year; *RET*: rearranged during transfection; ROS-1: c-ros oncogene 1; UK: United Kingdom.

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, administration requirements and costs of selpercatinib for advanced *RET* fusion-positive NSCLC is provided in Table 2.

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.[8] Administration of selpercatinib inhibits cell growth in tumour cells that exhibit increased *RET* activity[8]
Marketing authorisation/CE mark status	A conditional marketing authorisation application for selpercatinib for the treatment of *RET* fusion-positive NSCLC was submitted to the European Medicines Agency (EMA) on [redacted] and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Selpercatinib as monotherapy is indicated for the treatment of adults with: [redacted]
Method of administration and dosage	Oral 160 mg (2 x 80 mg capsules), BID. 40 mg capsules 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, this will involve NGS at designated Genomic Hubs
List price and average cost of a course of treatment	The list price of a 60 hard capsule pack of 80 mg or 40 mg selpercatinib is £[redacted]. The cost of a 28-day cycle of selpercatinib is £[redacted]
Patient access scheme (if applicable)	[redacted]

Abbreviations: BID: twice daily; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; NGS: next generation sequencing; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PAS: Patient Access Scheme; PASLU: Patient Access Scheme Liaison Unit; *RET*: rearranged during transfection.
Source: Selpercatinib Draft SmPC.[8]

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

Summary of the health condition

Disease overview

- Lung cancer is the third most common cancer in England.[9] NSCLC accounts for between 80–85% of lung cancer cases, with 1–2% of these cases estimated to exhibit a *RET*-fusion; this equates to an estimated 137 adults (first line: 102; second line: 35) testing positive in England and Wales in 2021[4, 10, 11]
- The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. Approximately 50% of cases are diagnosed at advanced stages in England, with only 40% of lung cancer patients, as a broad category, surviving >1 year following diagnosis.[10, 12] There is limited data on life expectancy for *RET* fusion-positive patients, although real-world evidence indicates that this may be similar to patients with other oncogenic drivers[13]
- 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.[14, 15] 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[16]
- Selpercatinib is a highly selective RET kinase inhibitor, that has shown promising activity in advanced *RET* fusion-positive solid tumours[17]

Clinical pathway

- Patients with *RET* fusion-positive NSCLC currently do not have access to a targeted therapy in England
- The transition to next generation sequencing panel tests for common oncogenic drivers (ALK translocation, EGFR mutation, ROS-1 rearrangements and *RET*) performed at Genomic Hubs in England, is anticipated to expedite the diagnostic process. This should allow clinicians to prescribe targeted therapies, like selpercatinib, as first line treatment[18]
- Platinum-based chemotherapy, immunotherapy or a combination of both are the conventional first line therapies recommended by NICE for advanced NSCLC cancers that do not exhibit recognised oncogenic rearrangements. Market share data indicates that immunotherapy is replacing chemotherapy in routine clinical practice. Pembrolizumab combination therapy had a high market share ([redacted]) in Q3 of 2019[19]
- For patients with advanced, non-squamous NSCLC who have progressed from first line therapy, several therapeutic options are indicated depending on the first line treatment received. Best supportive care is an option for those patients unfit for systemic therapy

Proposed position of selpercatinib

- Selpercatinib is appropriate for use as a first line treatment for patients with advanced, non-squamous, *RET* fusion-positive NSCLC, replacing treatments currently recommended at this treatment line. Based on market share data, it is expected that selpercatinib would primarily replace pembrolizumab combination therapy[19]
- Delays to identifying patients' *RET* status, resulting from insufficient biopsy yields during diagnosis, may necessitate use of selpercatinib in the second line setting.[10] Clinical instances may also arise where treatment needs to progress without waiting for confirmation of oncogenic driver status. Based on market share data and clinical feedback, selpercatinib would primarily replace pembrolizumab, nivolumab or atezolizumab monotherapy, or docetaxel with nintedanib[19]
- Should selpercatinib subsequently be recommended by NICE, it would be the first RET kinase inhibitor to be available in England and Wales and would fulfil an unmet need for a highly effective, targeted treatment for patients with advanced NSCLC whose cancers are driven by an oncogenic *RET* rearrangement

B.1.3.1 Disease Overview

Disease background

Lung cancer is the third most common cancer in England, accounting for 12.7% of all new cases, with 38,906 people newly diagnosed in England in 2017.[9] By gender, lung cancer is the second most common type of cancer for both males and females, and by age, it is classified in the top three most common cancers for men and women over 55 years.[9] Lung cancer is also the leading cause of cancer-related death in England, with an age-standardised mortality rate for women and men of 46.1 and 65.8, respectively per 100,000 in 2017.[9] As such, lung cancer represents a key clinical and public health challenge.[10, 20]

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 small cell lung cancer and NSCLC.[10] NSCLC accounts for the majority (80–85%)[21] of cases in 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 call undifferentiated carcinoma are frequently considered together under "non-squamous" histology and combined account for approximately 70% of NSCLC tumours.[10]

In addition, NSCLC can be further classified by genetic markers such as EGFR mutations, ALK translocation and ROS-1 rearrangements.[22] *RET* fusion-positive patients account for approximately 1–2% of NSCLC cases and are most commonly seen in adenocarcinoma, but have been reported in mixed adenosquamous histology.[4]

Rearranged during transfection tyrosine kinase

RET is a transmembrane receptor protein tyrosine kinase, which is present on the surface of several tissue types in the nervous system, adrenal medulla and thyroid.[4] The RET protein is encoded by the *RET* gene, which under normal circumstances plays a role in cell growth, division and specialisation.[23] 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.[24] 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.[25]

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.[4] This leads to abnormal activation of the protein and, in turn, downstream signalling in the cell, including activation of MAPK, PI3K/AKT and JAK/STAT pathways.[4] Abnormal *RET* activity enhances cell survival, proliferation, transformation, migration and angiogenesis, making *RET* fusions an important oncogenic driver in NSCLC.[26]

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.[4] Patients with *RET* fusion-positive NSCLC are typically of a younger age (≤60 years) with minimal or no prior history of smoking.[13] 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).[4, 13,]

[27] *RET* fusions in NSCLC tumours have also been found to be associated with female gender and Asian ethnicity.[4]

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).[10, 28, 29] In addition, *RET* fusions tend to be mutually exclusive with other major lung cancer oncogenic drivers and therefore represent a unique molecular target.[6]

Studies reporting epidemiological data for *RET* fusion-positive NSCLC are limited in number and by geography,[27] 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 and an upper estimate of 2% for the occurrence of *RET* fusions from O'Leary 2019, 102 patients are estimated to have advanced non-squamous NSCLC exhibiting a *RET* fusion molecular subtype in the first line setting, whilst 35 patients are estimated to present with *RET* fusions in the second line setting in England and Wales in 2021.[4, 11, 30, 31]

Disease progression and prognosis

The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. NSCLC can be categorised into four stages, with Stages IIIB (cancer spread to lymph nodes and other organs in the chest) and IV (cancer spread to other parts of the body) grouped under the classification "advanced". The five-year survival rate for those diagnosed in earlier stages of NSCLC disease is estimated to be between 53–78%, which decreases to 2–13% for those diagnosed at advanced stages.[32] 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.[10]

Nevertheless, a high proportion of NSCLC cases are currently diagnosed at an advanced stage in England (46.8% were diagnosed at Stage IV in 2017), primarily because of the ambiguity of common symptoms, which include fatigue, loss of appetite, cough and respiratory problems.[10, 12] 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.[33, 34] As a result, prognosis for lung cancer on the whole is poor, with only 40% of patients surviving >1 year following diagnosis between 2012–2015, compared with >95% of English patients with a breast or prostate cancer diagnosis.[10]

There is some evidence that prognosis for patients with *RET* fusion-positive NSCLC is similar to those with NSCLC expressing other oncogenic drivers. Data from the IMMUNOTARGET registry of patients diagnosed with advanced NSCLC compared PFS and OS from treatment initiation for different molecular subtypes of NSCLC (N = 551 from 10 countries).[13] Median PFS ranged between 2.1–3.4 months, whilst median OS ranged between 10.0–21.3.[13] 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.[13]

Brain metastases also 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.[35] 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).[36]

Burden of disease

NSCLC represents a humanistic and economic burden on society. Disease caused by NSCLC, and the various therapies used to cure or manage it, impact the emotional and physical functioning of patients.[37, 38] However, there is a paucity of data on the HRQoL impact of *RET* fusion-positive NSCLC specifically. As such, the data presented here relates to NSCLC, regardless of genomic alteration and/or biomarker expression, although this is anticipated to also represent 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.[39] However, as NSCLC progresses, patients experience greater symptom burden and subsequently lower quality of life.[40] Common physical symptoms of NSCLC include fatigue (98%), loss of appetite (98%), respiratory problems (94%), cough (93%), pain (90%) and blood in sputum (70%).[37] 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.[41]

The impact of NSCLC on physical HRQoL and functional status largely is related to these symptoms. However, diagnosis, treatment and conversations around prognosis also impact the mental health of patients, with depression reportedly affecting between 23–40% of patients, whilst anxiety affects an estimated 16–23% of patients.[37] In addition, physical symptoms of the disease can cause distress, fatigue and create sleep problems that reduce cognitive functioning.[37] As a result of this impact on their physical and mental wellbeing, patients are increasingly unable to complete activities perceived as "normal" in their family and social roles.[37]

Consequently, the HRQoL in NSCLC patients is lower than in the general population.[14] A 2018 systematic review highlighted that among patients receiving second line treatment for advanced NSCLC, mean EuroQol-5D (EQ-5D) scores ranged between 0.53–0.82, with the highest values being associated with tyrosine kinase inhibitor treatment.[14] A similar range was seen among patients being treated for advanced NSCLC, where the treatment line was unspecified (0.53–0.77).[14] 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).[14] All scores were lower than the index EQ-5D score, calculated for the English general population (0.85).[15]

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.[16] 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.[42] 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.[43] Due to the impact of NSCLC on patients' mental and physical health, their work life is also negatively affected, leading to indirect costs to society through absenteeism, lost productivity and early retirement.[27]

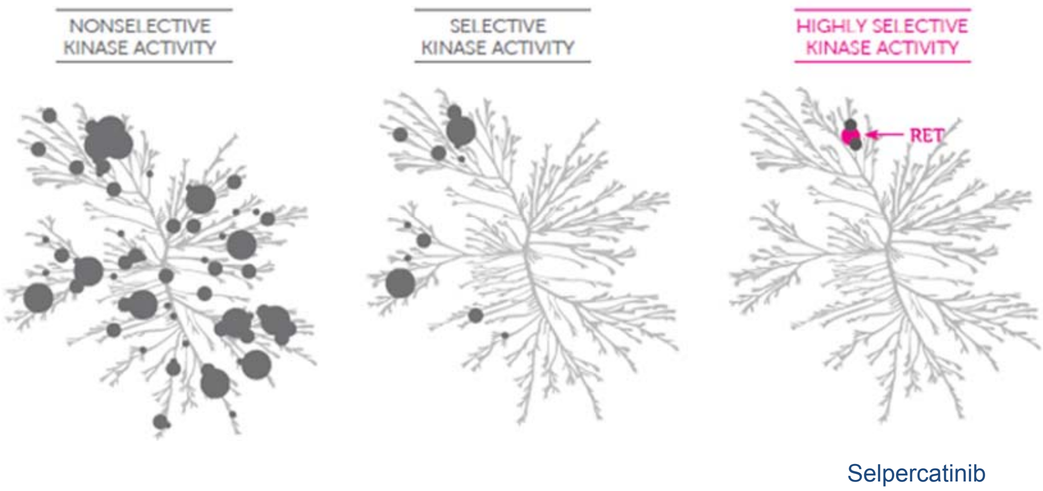
Selpercatinib

Selpercatinib is a highly selective inhibitor of fusion, mutant and wild-type products involving the proto-oncogene receptor tyrosine kinase RET.[44] The drug acts as an inhibitor that controls the RET kinase enzyme and prevents tumour cell growth.[44] Selpercatinib has shown promising activity in advanced *RET*-positive solid tumours and is reportedly 250-fold more selective for RET relative to other kinases (Figure 1).[17] 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.[4] Due to *RET* fusions predominantly occurring with lung adenocarcinoma, it is anticipated for selpercatinib to be used in patients with non-squamous histology only.[4]

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. 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 patients treated with 160 mg BID and the anti-tumour activity of selpercatinib analysed.[45] Both first line and second line patients with *RET* fusion-positive advanced NSCLC were included within the Phase II stage of the trial.

Due to the anticipated benefit to patients' health to be realised through the early licensing of selpercatinib, Eli Lilly and Company have applied for conditional marketing authorisation from the EMA for adult patients with advanced *RET* fusion-positive NSCLC. Should selpercatinib subsequently be recommended by NICE, it would be the first RET kinase inhibitor to be available in England and Wales, and would fulfil an unmet need for a highly effective (see Section B.2), targeted treatment for 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



Note: 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).[17]

B.1.3.2 Clinical pathway of care

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

The treatment of NSCLC in the UK has been assessed by NICE through both published guidelines (NG122) and previous technology appraisals (TAs).[22] Given that selpercatinib is anticipated to be the first RET kinase inhibitor on the market, NICE have not yet published any guidance specifically for *RET* fusion-positive NSCLC. The treatment pathway for *RET* fusion-positive NSCLC described below has therefore been informed by current guidance available from NICE for the treatment of NSCLC more widely.

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 (i.e. PD-L1 status; an immune checkpoint protein expressed on the surface of cancer cells).[10, 22] Biopsy for histological or cytological confirmation is therefore important for diagnosis and informing treatment decisions.[10] In England, key oncogenic drivers in NSCLC (EGFR, ROS1 and ALK) were previously identified using fluorescence in-situ hybridisation (FISH) performed on biopsy samples sequentially, increasing the time taken to make a molecular diagnosis. However, the ongoing transition to NGS, completed in Genomic Hubs, will mean a panel of genetic mutations, rearrangements and fusions (including *RET*-fusions) can be identified.[18] This will expedite the diagnostic process and allow clinicians to use targeted therapies, like selpercatinib, as first line treatment.

For patients diagnosed with early stage NSCLC (Stage I–IIIA), treatments with curative intent are indicated. These include surgery, radiotherapy, chemoradiotherapy and multimodality treatment.[22] However, for patients who present with, or progress to, advanced (Stage IIIB or IV) NSCLC, treatments with curative intent are not suitable, and NICE recommends systemic anti-cancer therapies, with treatment choice informed by the histology of the patient's tumour (squamous versus non-squamous), and with targeted treatments recommended for those patients presenting with recognised genetic markers.[22]

It is standard clinical practice for patients with identified and treatable genetic markers to receive treatments targeted at that genetic marker, rather than by their biomarker status (i.e. PD-L1 <50% or ≥50%). However, given that there are currently no treatments available in the UK that target *RET* fusion-positive NSCLC, 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 patients, typically have just one genetic marker, and thus would not benefit from other oncogene targeted therapies.[27, 46] As described previously, *RET* fusion-positive patients are predominantly of non-squamous histology.[4] NICE recommends a number of therapy options for patients without genetic markers presenting with first line (untreated), advanced, non-squamous NSCLC, as presented in Figure 4. For patients who do not express any genetic markers nor tumour protein markers (e.g. PD-L1) in the first line setting, NICE recommends treatment with pembrolizumab combination therapy, which is currently under the CDF (TA557) and is being reviewed for exit (ID1584).[47, 48] A market share study performed by Eli Lilly and Company for all non-squamous NSCLC, which included drugs for other genetic markers, found that pembrolizumab combination therapy had a market share of [redacted] in Q3 2019, giving it the highest market share of therapies recommended for cancers expressing no genetic or protein markers.[19]

For patients with tumours expressing various levels of PD-L1, NICE recommends a number of therapy options in the first line setting. This includes pembrolizumab monotherapy, which is recommended for patients with a PD-L1 tumour proportion score (TPS) of ≥50% (TA531).[49] Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel (atezolizumab combination therapy) (TA584),[50] pemetrexed in combination with carboplatin (NG122)[22] and platinum doublet chemotherapy (NG122 or TA181)[22, 51] with or without subsequent pemetrexed maintenance therapy (TA402 or TA190)[52, 53] are recommended for patients with a PD-L1 TPS of <50%. According to market share data collected by Eli Lilly and Company, pembrolizumab [redacted]) in Q3 2019. Pemetrexed in combination with platinum chemotherapy (either carboplatin or cisplatin) had a market share of [redacted], whilst gemcitabine in combination with platinum chemotherapy had a market share of [redacted]. All other therapies, either monotherapies or combinations, with market share under 1% were grouped. "Other monotherapies" had a combined market share of [redacted] while "other combinations" have a market share of [redacted]. Market share data for top first line treatment regimens in non-squamous NSCLC in the UK are summarised in Figure 2.

Figure 2. Recent market share data for first line treatment regimen in non-squamous NSCLC in the UK

[redacted]

*May include targeted therapies
Notes 1: Base (treatment cases): Q3 2019: 218; Q2 2018: 203; Q2 2017: 191; Q4 2016: 210
Notes 2: Data labels are shown for the most recent time estimate available (Q3 2019)
Source: Eli Lilly and Company Ltd. Data on File.

For patients with advanced, non-squamous NSCLC who have progressed from first line therapy to second line and beyond, NICE recommends a number of therapeutic options, as presented in Figure 4.

With the exception of pembrolizumab and nivolumab, which are recommended in patients with PD-L1 TPS ≥1% (TA428 and TA484), the remainder of therapies for second line patients are biomarker-independent. Nivolumab (TA484) is currently recommended under the CDF, however, it is under appraisal for exit with a draft positive recommendation currently under consultation pending final publication on 21 October 2020 [ID1572]. Therapies recommended by NICE for treatment of patients following first line chemotherapy, regardless of PD-L1 status, include atezolizumab (TA520) and nintedanib in combination with docetaxel, or docetaxel monotherapy (TA347). NICE also recommends treatment with pemetrexed in combination with carboplatin or other platinum doublet chemotherapy (NG122) with or without subsequent pemetrexed maintenance therapy (TA402 or TA190) following pembrolizumab monotherapy (TA531). Following treatment with systemic anti-cancer therapies, or should patients not wish to receive active therapy, patients may receive best supportive care.

Market share data collected by Eli Lilly and Company suggests that of therapies used at second line for NSCLC, atezolizumab monotherapy had the highest share in Q3 of 2019 ([redacted]). Pembrolizumab monotherapy also had a high market share ([redacted]), alongside nintedanib combined with docetaxel ([redacted]), docetaxel monotherapy ([redacted]) and nivolumab ([redacted]). Platinum doublet chemotherapy (e.g. gemcitabine and carboplatin) had a lower market share ([redacted]), alongside pemetrexed and cisplatin ([redacted]) and pemetrexed and carboplatin ([redacted]). Market share data for top second line treatment regimens, including drugs for other genetic markers, in non-squamous NSCLC in the UK are summarised in

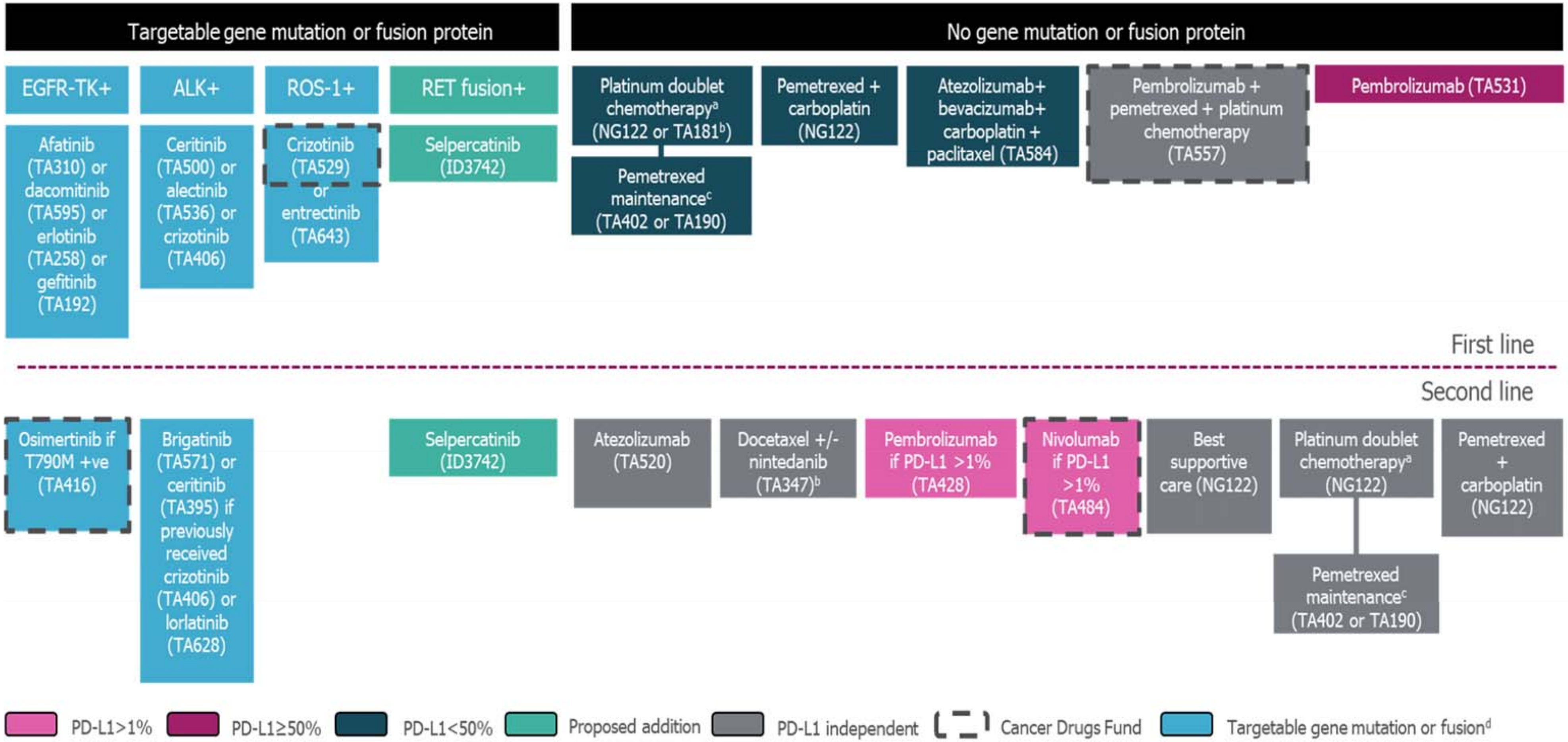
Figure 3.

Figure 3. Recent market share data for second line treatment regimen in non-squamous NSCLC in the UK

[redacted]

*May include targeted therapies
Notes 1: Base (treatment cases): Q3 2019: 218; Q2 2018: 203; Q2 2017: 191; Q4 2016: 210
Notes 2: Data labels are shown for the most recent time estimate available (Q3 2019)
Source: Eli Lilly and Company Ltd. Data on File.

Figure 4. NICE-recommended treatment pathway for advanced, non-squamous, NSCLC



[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 and adenocarcinoma, respectively.
[c]Pemetrexed maintenance is only permitted after pemetrexed + cisplatin (not carboplatin).
[d]Other targeted treatments are represented in the pathway for illustrative purposes but are not indicated for patients with *RET* fusion-positive NSCLC.
Abbreviations: ALK: anaplastic lymphoma kinase; EGFR-TK: epidermal growth factor receptor tyrosine kinase; PD-L1: programmed death-ligand; *RET*: rearranged during transfection; ROS-1; c-ros oncogene 1.

Positioning of selpercatinib relative to the current treatment pathway

Selpercatinib, as a selective tyrosine kinase inhibitor (TKI) that targets *RET*-fusion positive tumours, would be positioned as a first line treatment option for patients diagnosed with Stage IIIB and IV non-squamous *RET* fusion-positive NSCLC. As selpercatinib will be the first *RET* specific treatment available for these patients, it will fundamentally alter the current treatment pathway by introducing a new treatable genetic marker. Consequently, there is no true comparator for selpercatinib. In practice, selpercatinib is anticipated to substitute first line non-targeted treatments, such as pembrolizumab combination therapy (TA557), for those patients with a positive *RET* status.

Although molecular testing at Genomic Hubs should allow most patients to receive their *RET* status prior to initiating treatment, delays may occur if initial biopsy yield is insufficient for testing or if there is a clinical need to treat the patient prior to receipt of the test result.[10] Selpercatinib may therefore be positioned as a second line treatment for those patients who received previous therapies prior to confirmation of *RET* status, primarily replacing non-targeted treatments such as pembrolizumab monotherapy (TA428) and nivolumab monotherapy (TA484). A discussion of comparator treatments is presented in Section 0.

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

Targeted treatment options for *RET* fusion-positive NSCLC, which offer improved clinical effectiveness and tolerability compared with currently available treatments, represent an unmet medical need. There are currently no approved targeted therapies for this indication available on the NHS. Patients with advanced *RET* fusion-positive NSCLC instead receive the same treatment options as those patients with no recognised oncogenic drivers.

As outlined in the treatment pathway (Figure 4), immunotherapies are the first line conventional pharmacological therapy for advanced, non-squamous NSCLC cancers without recognised mutations or fusions. Non-targeted chemotherapies are another option, although market share data indicates declining use in clinical practice due to the preferential use of immunotherapy.[19] A real-world study of patient outcomes in the UK found that 45% of NSCLC patients treated with first line chemotherapy subsequently received second line therapy.[54] The median time to progression was five months and median survival was 10 months.[54] In addition, the toxic and systemic nature of chemotherapy regimens means patients are highly likely to suffer from side effects, which can significantly impact patients' quality of life. The use of immunotherapy has provided additional treatment options for NSCLC patients, although response rates remain below 50% in trials (CheckMate057: nivolumab ORR = 19%; KEYNOTE-189: pembrolizumab + chemotherapy ORR = 47.6%).[55] In addition, adverse events from immunotherapies can affect one or several different systemic organ system, with an incidence of Grade 3 and higher toxicities of 7–13%.[55]

Use of multi-target tyrosine kinase inhibitors (MKIs) has been trialled for *RET* fusion-positive tumours, although use of MKIs by the NHS has not been approved.[4, 26] MKIs have demonstrated limited efficacy, with an ORR ranging between 16%–53% and a PFS of 2.2–7.3 months, as well as concerning rates of high-grade toxicity due to off-target kinase inhibition.[4, 26] RET kinase inhibitors with a higher specificity, like selpercatinib, therefore represent the most promising treatment option for patients with advanced *RET* fusion-positive NSCLC and are anticipated to bring benefits to patients in the NHS through improved efficacy and reduced toxicity, compared with non-targeted chemotherapy.[4]

B.1.4 *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 compared to 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.

In the technology appraisal of entrectinib for treating ROS1-positive advanced NSCLC (TA643), concerns related to inequitable access to targeted treatments, due to regional variation in molecular testing practices, were addressed.[56] In England, the transition to NGS testing, completed at seven Genomic Hubs, means *RET* rearrangements can be tested for routinely alongside other oncogenic drivers in a standardised manner across different centres. This equality consideration should therefore not be a concern in this submission.

B.2 Clinical effectiveness

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

- The efficacy of selpercatinib in *RET* fusion-positive NSCLC has been demonstrated in LIBRETTO-001, a first in-human Phase I/II open-label trial[57]
- The primary endpoint used in LIBRETTO-001 was objective response rate (ORR), defined as the proportion of patients with a best objective response (BOR) of confirmed complete response (CR) or partial response (PR) based on RECIST v1.1 and Independent Review Committee (IRC) assessment:[57]
    - In the **first line** trial population (Supplemental Analysis Set 1 [SAS1]) the **ORR** was 85% (33/39, 95% CI: 69.5–94.1)
    - In the **second line** trial population (Primary Analysis Set [PAS]) the **ORR** was 64% (67/105; 95% CI: 53.9–73.0)
    - In the **second line** trial population (Integrated Analysis Set [IAS]) the **ORR** was [redacted] ([redacted])
    - Selpercatinib treatment resulted in high tumour response rates in both first and second line *RET* fusion-positive NSCLC patients, decreasing tumour size and delaying disease progression
- Key secondary outcomes assessed during LIBRETTO-001 included duration of response (DOR), PFS and OS by IRC assessment:
    - In the **first line** (SAS1) trial population, the **median DOR** was not reached (95% CI: 12.0–not estimable [NE]) at the time of data cut-off, with death or progressive disease (PD) observed in only [redacted] patients in a median follow-up of 7.4 months[57]
    - In the **second line** (PAS) trial population, the **median DOR** was 17.5 months (95% CI: 12.0–NE), with death or disease progression observed for [redacted]) patients in a median follow-up of 12.1 months[57]
    - In the **second line** (IAS) trial population, the **median DOR** was [redacted] months ([redacted]), with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
    - In the **first line** (SAS1) trial population, the **median PFS** by IRC assessment was not reached (95% CI: 13.8–NE), with death or disease progression only reported in [redacted]) patients in a median follow-up of 9.2 months
    - In the **second line** (PAS) trial population, the **median PFS** was 16.5 months (95% CI: 13.7–NE), with death or disease progression observed in [redacted]) patients in a median follow-up of 13.9 months
    - In the **second line** (IAS) trial population, the **median PFS** was [redacted] months ([redacted], with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
    - In the **first line** (SAS1) trial population, the **median OS** was not reached ([redacted] at the 16th December 2019 data cut-off, with only [redacted]) death reported in a median follow-up of [redacted] months
    - In the **second line** (PAS) trial population, the **median OS** was not reached ([redacted]. Death was observed in [redacted] patients in a median follow-up of [redacted] months
    - In the **second line** (IAS) trial population, the **median OS** was [redacted] ([redacted]). Death was observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
    - Across first line and second line trial populations, results indicated that the high response rates observed with selpercatinib administration were durable in a high proportion of first and second line *RET* fusion-positive NSCLC patients, thereby

maintaining their HRQoL levels for longer. Preliminary OS estimates suggest good survival rates for patients treated with selpercatinib

- Patient reported outcomes were assessed using the European Platform of Cancer Research Quality of Life Questions C30 (EORTC QLQ-C30):
    - o Patients experienced definite improvements in QLQ-C30 sub scores: physical ([redacted] emotional [redacted] role [redacted] cognitive [redacted] and social function [redacted]. There was a median time to definite improvement amongst NSCLC patients of [redacted] months
    - o In general, a higher proportion of NSCLC patients reported improved, rather than worsening, QLQ-C30 scores, with [redacted] versus [redacted] of patients reporting improved versus worsened global health status scores during Cycle 9 of selpercatinib treatment
    - o In line with clinical effectiveness measures, QLQ-C30 scores indicate a benefit to quality of life for advanced *RET* fusion-positive NSCLC patients receiving selpercatinib
- The results of LIBRETTO-001 demonstrate that treatment with selpercatinib results in a high and durable response rate for both first and second line *RET* fusion-positive NSCLC patients and corresponds with benefits to patients' HRQoL[57]

Summary of indirect treatment comparisons

- 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. An indirect treatment comparison was therefore necessary to compare selpercatinib to other first and second line treatments that were relevant to the decision problem
- In the first line treatment setting, ORR, PFS and OS were modelled. Both random effects (RE) and fixed effects (FE) models were assessed for all outcomes
- Results of the RE model are reported for **ORR** in the first line setting for the overall population and the FE model in the PD-L1≥50% subgroup
    - o Selpercatinib demonstrated the highest odds of inducing a tumour response (**ORR**) compared to pemetrexed plus platinum chemotherapy (odds ratio [OR]: [redacted]; 95% credible intervals [CrI]: [redacted]) of all treatments included in the analysis
    - o For the subgroup analysis of pembrolizumab monotherapy in patients with PD-L1≥50%, the FE model was used due to poor convergence of the RE model
- Results for a RE model with informative prior results are presented for the first line treatment setting for both **PFS and OS**:
    - o Selpercatinib demonstrated the lowest risk of disease progression (**PFS**) compared to pemetrexed plus platinum chemotherapy (hazard ratio [HR]: [redacted]; [redacted]) of all treatments included in the analysis
    - o Selpercatinib demonstrated the lowest risk of death (**OS**) compared to pemetrexed plus platinum chemotherapy (HR: [redacted]; 95% CrI: [redacted]) of all treatments included in the analysis
- In the second line treatment setting, a hierarchical exchange model was used to take account of PD-L1 as a class in the model. Age was significant and included in the model; the results were centred on [redacted] years of age (the mean age of the second and subsequent line NSCLC population in LIBRETTO-001):
    - o Selpercatinib demonstrated the highest odds of inducing a tumour response (**ORR**) compared to docetaxel (OR: [redacted])
    - o Selpercatinib demonstrated the lowest risk of disease progression (**PFS**) compared to docetaxel (HR: [redacted] of all treatments included in the analysis
    - o Selpercatinib demonstrated the lowest risk of death (**OS**) compared to docetaxel (HR: [redacted] of all treatments included in the analysis

Summary of adverse events

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (regardless

of tumour type or treatment history) and specifically in those patients with *RET* fusion-positive NSCLC:
  - In the Overall Safety Analysis Set (OSAS) and the *RET* fusion-positive NSCLC Safety Analysis Set (SAS), permanent discontinuation of selpercatinib due to treatment-emergent adverse event (TEAE) were infrequent ([redacted]), with no predominant pattern among the individual adverse events (AEs) reported
  - Grade 3 or 4 TEAEs were reported in [redacted] OSAS patients and [redacted] *RET* fusion-positive NSCLC SAS patients, irrespective of relatedness to selpercatinib. 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

Innovation

- There are currently no targeted therapeutic options available on the NHS for *RET* fusion-positive NSCLC patients in either the first line or second line setting
- Selpercatinib has demonstrated clinical benefit by directly targeting *RET* as an underlying driver of disease amongst patients with *RET* fusion-positive NSCLC. The magnitude, durability and speed of the response rate observed in the LIBRETTO-001 trial represents a therapeutic innovation, with the potential to prolong patient quality of life
- Selpercatinib is administered orally whereas commonly used chemotherapies (e.g. pemetrexed) and immunotherapies (e.g. pembrolizumab) are administered intravenously. Oral administration can allow cost savings attributable to the reduction in resource utilisation provided by self-administration at home and is often more acceptable to the patient

Interpretation and conclusions

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

B.2.1 *Identification and selection of relevant studies*

Systematic literature reviews (SLRs) were conducted to identify relevant clinical evidence on the the efficacy and safety of selpercatinib in *RET*-altered solid tumours, including adults with first line and second line advanced *RET* fusion-positive NSCLC who require systemic therapy. The original SLR for first line NSCLC was conducted in June 2018, with an update currently in progress. The SLR for second line NSCLC was conducted in September 2019.

In total, the first line NSCLC SLR identified [redacted] studies in 30 peer-reviewed publications and 6 conference abstracts. Two studies were published as conference abstracts only. The publication year of the included studies ranged from 2004 to 2018, with most being published within the last 4 years. The second line NSCLC SLR identified [redacted] studies ([redacted] primary reports; 12 of which were trials including patients with *RET*-altered tumours). This SLR used a previous SLR (Vickers et al [2019]) to identify relevant studies; [redacted] relevant studies were identified in Vickers et al (2019).[58] Full details of the SLR search strategy, study selection process and results for both the first and second line can be found in Appendix D.

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, 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 selpercatinib efficacy and safety 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 3.

The eligibility criteria for the LIBRETTO-001 trial was 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 this study is in line with the population of relevance for this submission: 'adults with advanced *RET* fusion-positive NSCLC who require systemic therapy'.

Table 3. Clinical effectiveness evidence

<table>
<tr><th>Study</th><th colspan="3">LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[1]</th></tr>
<tr><td>Study design</td><td colspan="3">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)</td></tr>
<tr><td>Population</td><td colspan="3">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 16th December 2019, N = [redacted] patients had been enrolled onto the trial, of which N = 329 were NSCLC patients

First line (untreated) or second line (pre-treated) RET fusion-positive NSCLC patients are the focus of this submission</td></tr>
<tr><td>Intervention(s)</td><td colspan="3">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</td></tr>
<tr><td>Comparator(s)</td><td colspan="3">N/A</td></tr>
<tr><td>Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>Indicate if trial used in the economic model</td><td>Yes</td></tr>
<tr><td>Rationale for use in the model</td><td colspan="3">LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with first line or second line RET-fusion positive NSCLC</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="3">Measures of disease severity and symptom control:
• ORR
• PFS
• OS
HRQoL:
• EORTC QLQ-C30
Safety outcomes:
• AEs</td></tr>
<tr><td>All other reported outcomes</td><td colspan="3">• DOR</td></tr>
</table>

Abbreviations: AEs: adverse events; BID: twice daily; CNS: central nervous system; 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; 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 (16th December 2019 cut-off),[45] Drillon et al. 2020[57]

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

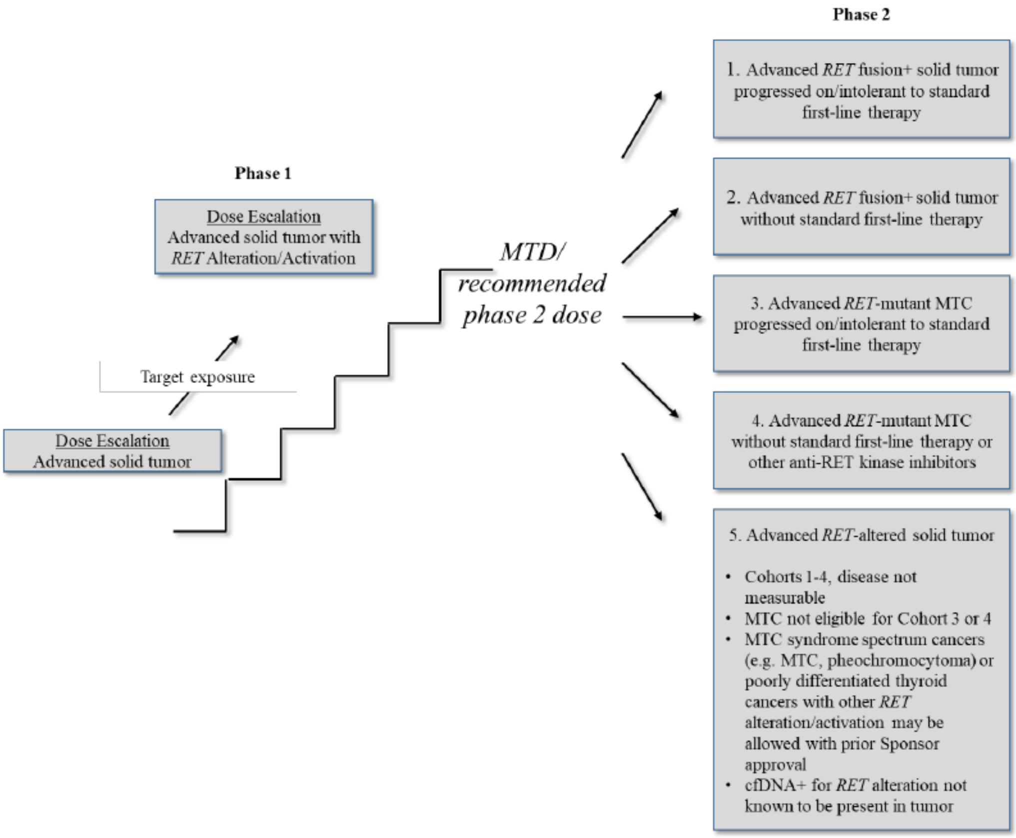
B.2.3.1 Trial design

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 solid tumours (including NSCLC), *RET*-mutant MTC and other tumours with *RET* activation.[57] The patient population includes patients as young as 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 5, 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 assessed. The study is currently in Phase II.[1] A schematic of the trial is presented in Figure 5. The most recent data cut-off for the interim analysis was 16th December 2019.

Figure 5. 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. 2020, Study Protocol.[59]

The primary objective of Phase I was to determine the MTD and the recommended Phase II dose (RP2D). During Phase I dose escalation, patients received selpercatinib dose levels that ranged from 20 mg once daily (QD) to 240 mg twice daily (BID), depending upon dose level assignment upon entry into the trial (total daily dose ranged between 20 and 480 mg).[59] A classical 3+3 dose escalation design was used, with 3 to 6 patients enrolled in each dose level cohort.[60] The starting dose of selpercatinib in oral capsule form was 20 mg QD for 1 Cycle. Cycles lasted 28-days. Escalation was to proceed through all dose levels or until the Safety Review Committee (SRC) and Sponsor determined that a suitable dose was achieved based on available data (safety, PK exposure, clinical activity).[59] Dose escalations were in increments of 100% above the previous dose level for the first 3 dose escalations. After the third dose increase, a modified Fibonacci dose escalation, where increments become smaller as the dose increases, was employed for any subsequent dose escalations, with increments of ~67%, ~50% and ~33%.[60] Additional dose escalations, if needed, were in increments of ~33%.[59] Each dose level after the starting dose represented the maximum dose to which patients were to be escalated, and no individual dose escalation was to be more than twice the dose at the previous level. Based on results from Phase I, the SRC selected an RP2D of 160 mg.

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 4).

Table 4. 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 *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

Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.

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 4). Individual patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity or other reasons for treatment discontinuation.[59] The primary endpoint for the Phase II portion of the trial was ORR using RECIST v1.1. Secondary ontological 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 patients with *RET* fusion-positive NSCLC in the first line and second line treatment setting 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 5.

Table 5. Summary of LIBRETTO-001 trial methodology

Trial name	**LIBRETTO-001**
Location	A total of 84 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 (a positive germline test for a *RET* mutation was acceptable for patients with MTC) • 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, and was administered QD or BID, depending upon dose level assignment. 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 o 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 PAS population (see Table 6, Section B.2.3.3 for a definition of this analysis set): • 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 PAS population: • Fusion partner: o KIF5B o CCDC6 o NCOA4 o KIAA1468 o ARHGAP12 o CCDC88C o CLIP1 o PRKAR1A o RBPM and DOCK 1 o TRIM24 o Other o Unknown • Molecular assay: o NGS on blood or plasma o NGS on tumour o PCR o Other The primary objective was also analysed by number of previous therapies or type of prior therapy received: • Number of prior therapies (1–2 versus 3) • Prior anti-PD-1/PD-L1 therapy (yes versus no) • Prior multi-kinase inhibitor (yes versus no)
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 16th December 2019, the median follow-up was [redacted], [redacted] and [redacted] months for OS in patients in the SAS1, PAS and Integrated Analysis Set (IAS), respectively. See Table 6, Section B.2.3.3 for definitions of the SAS1, PAS and IAS populations Individual 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: Drilon et al. 2020, Study Protocol.[59], Drilon et al. 2020[57]

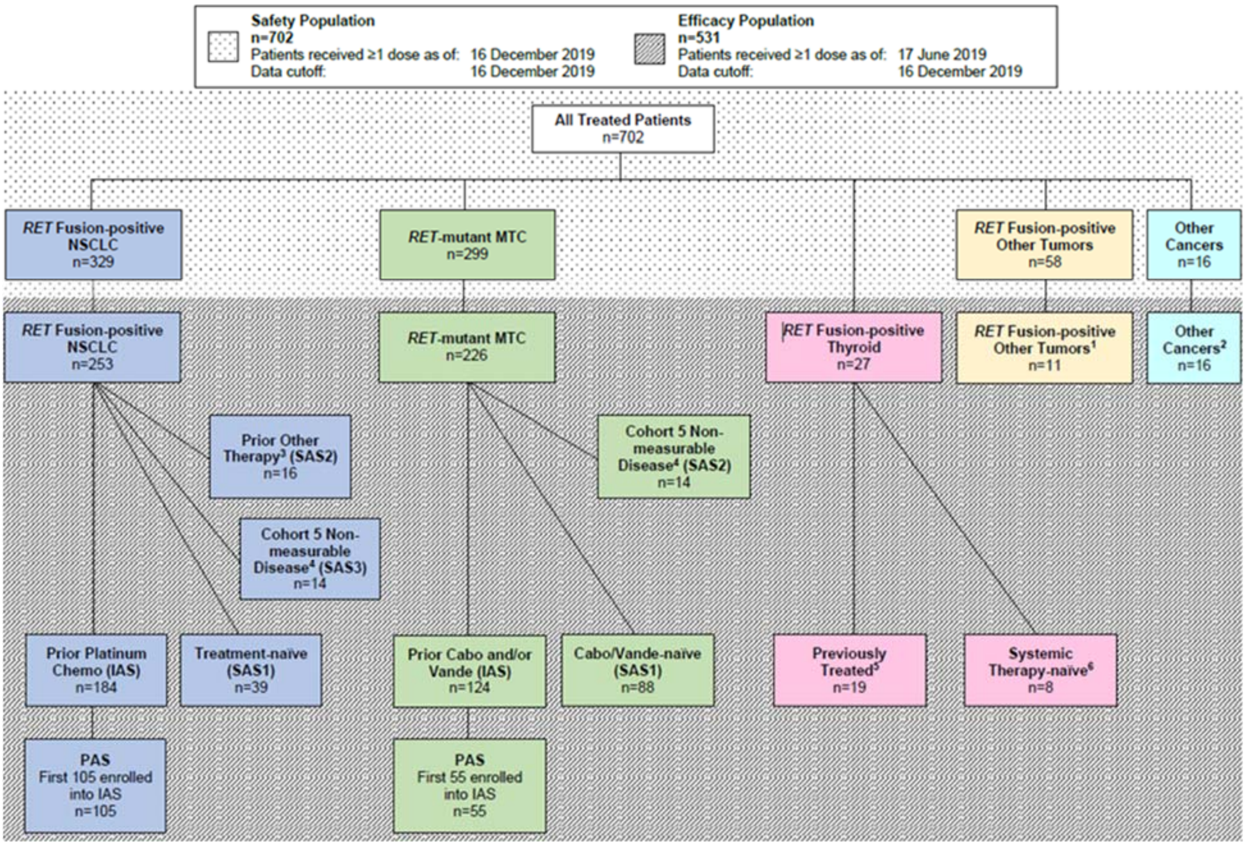
B.2.3.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets

For the purposes of analysis, efficacy data sets were categorised into broad groupings of patients with *RET* fusion-positive NSCLC, *RET*-mutant MTC and *RET* fusion-positive thyroid cancer, as well by whether prior treatment had been received (Figure 6).[59] Definitions for each analysis set are presented in Table 6.

There were 5 analysis sets for patients with NSCLC. Only clinical effectiveness data from first line (treatment-naïve) and second line (pre-treated) patients, with measurable disease, are considered in this submission, in line with the decision problem. These patients comprised the SAS1 (first line), PAS (second line) and IAS (second line) populations.[59] Baseline characteristics (Section B.2.3.4) are considered for all 5 analysis sets.

Figure 6. Enrolment and derivation of analysis sets in LIBRETTO-001



Footnotes: [1]*RET* fusion-positive other tumours: pancreatic cancer, rectal neuroendocrine cancer, salivary gland cancer, carcinoid, colon, small intestine, and xanthogranuloma. [2]Other solid tumours that do not fit the other disease cohorts. [3]Prior systemic therapy other than platinum-based chemotherapy. [4]Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 or Phase II Cohort 5. [5]Previously treated *RET* fusion-positive thyroid cancer defined as ≥1 prior systemic therapy in addition to radioactive iodine, if indicated. [6]Systemic therapy-naïve *RET* fusion-positive thyroid cancer defined as 0 prior systemic therapy other than radioactive iodine, if indicated.
Abbreviations: cabo: cabozantinib; IAS: Integrated Analysis Set; MTC: medullary thyroid cancer; n: number of patients within category; NSCLC: non-small cell lung cancer; PAS: primary analysis set; *RET*: rearranged during transfection; SAS: supplemental analysis set; vande: vandetanib.
Source: Drilon et al. 2020, Study Protocol.[59]

Table 6. 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[a] by RECIST v1.1 by IA 3. Received 1 or more lines of prior platinum-based chemotherapy 4. 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 1–4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off		184
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 (first line):** • No prior systemic therapy	39
		SAS2 (prior other systemic therapy): • Received prior systemic therapy other than platinum-based chemotherapy	16
		SAS3 (non-measurable disease): • No measurable disease[b]	14
Safety analysis			
Overall Safety Analysis Set	Patients treated with selpercatinib as of a data cut-off of 16th December 2019	**NSCLC Safety Analysis Set:** *RET* fusion-positive NSCLC	329
		RET-mutant MTC	[redacted]
		RET fusion-positive thyroid cancers	[redacted]
		RET fusion-positive other cancers	[redacted]
		Other cancers	[redacted]
		Total	[redacted]

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 Tumors, 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 (16th December 2019 cut-off); Drilon et al. 2020, Study Protocol.[59],[45]

Summary of clinical data cut-off dates

An interim analysis was conducted for 531 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 17th June 2019 data cut-off.[45] Unless noted otherwise, the results presented and analysed in this submission are based on a pre-planned analysis of efficacy and safety data from a 16th December 2019 data cut-off. The 16th December 2019 data cut-off provides an additional 6-months follow-up for safety and efficacy information for the 531 patients originally enrolled in LIBRETTO-001 as of 17th June 2019 enrolment date; of these patients, [redacted] were treated at the RP2D of 160 mg twice daily. Efficacy data for new patients enrolled into LIBRETTO-001 between 18th June 2019 and 16th December 2019 are not included in this discussion. The safety evaluable data set includes all [redacted] patients treated with selpercatinib as of the 16th December 2019 data cut-off.

Statistical methods

Table 7. 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 per starting dose may not provide dose-response information, given that intra-patient dose escalation was allowed during Phase I. Therefore, 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 • 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)
Sample size, power calculation	**Phase I** • Three to six patients were to be enrolled in each dose cohort based on a 3+3 design. Each patient was to participate in only a single dose cohort for the purpose of dose limiting toxicity (DLT) evaluation (however, after completion of the DLT evaluation period, intra-patient dose escalation was allowed, provided that the patient was tolerating their current dose, and the dose level to which the patient was escalated to had already been evaluated, had a DLT rate of <33%, and was declared safe by the SRC)

	• A starting sample size of at least three patients per dose cohort, expanding to six patients in the event of a marginal DLT rate (30%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e. observing two or more patients with DLT). If a true DLT rate of 50% was assumed, then there would be an 89% chance that dose escalation would be halted in a given cohort • During Phase I, selected dose cohorts previously declared safe by the SRC could be expanded to a total of approximately 15 patients to further investigate the tolerability, PK and biological activity of selpercatinib • 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 1 (patients with *RET* fusion-positive solid tumours who progressed on or were intolerant to standard first line therapy for their cancers), a true ORR of ≥50% was hypothesised when selpercatinib was administered to patients with such malignancies. A sample size of 55 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 30%. Ruling out a lower limit of 30% was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly defined patient populations who have failed prior therapies • For Cohort 2 (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% • For Cohort 3 (patients with *RET*-mutant MTC who progressed on or were intolerant to vandetanib and/or cabozantinib), a true ORR of ≥35% was hypothesised when selpercatinib was administered to such patients. A sample size of 83 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 20%. Ruling out a lower limit of 20% was considered clinically meaningful in patients who have failed prior MKI therapy (e.g. cabozantinib) and currently have limited treatment options for their advancing disease • For Cohort 4 (patients with *RET*-mutant MTC who are MKI-naïve), a true ORR of ≥50% was hypothesised when selpercatinib was administered to such patients. A sample size of 55 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 30%

	• With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% was 77.9% and 95.2%, respectively. Up to ~150 patients in Cohort 1 would be allowed to accommodate enrolment of other *RET* fusion-positive solid tumours
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 o 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 o 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 o 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) o Censored at the date of the first dose of selpercatinib • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression o 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 o 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 o 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.

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib in the first line and second line setting for *RET* fusion-positive NSCLC patients. Definitions for these outcome measures are presented in Table 8.

Table 8. 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:[61] • **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 clinically meaningful difference was defined as 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[62] Patients with "improvement" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients with "worsening" were defined as those who demonstrated a decrease by ≥10-points from their baseline score. A definite 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.

B.2.3.4 Baseline characteristics

A summary of patient demographics and other baseline characteristics for the 253 efficacy patients with NSCLC enrolled in LIBRETTO-001 is provided below.[45] Focus is placed on discussing the summary characteristics of the patients comprising the three analysis sets for which efficacy data will be presented (i.e. SAS1, PAS and IAS), although data from the SAS2 and SAS3 populations are presented in the tables to illustrate how the total values have been calculated.

Overall, patient demographics were similar across the populations of interest. The median age of all patients with *RET* fusion-positive NSCLC was 61 (range: 23–86) years (Table 9).[45] Across the three population of interest, the most common age range was 45–64 years; [redacted] of patients in the PAS, [redacted] in the IAS and [redacted] in the SAS1 population fell into this age category, respectively. All populations of interest had a higher proportion of females than males (59.0%, [redacted] and 56.4% patients were female in the PAS, IAS and SAS1, respectively). Overall, the majority ([redacted]) of *RET* fusion-positive NSCLC patients were white, with a high proportion of patients identified as Asian ([redacted]). Overall, most participants ([redacted] reported never smoking, with 71%, [redacted] and 74% of patients reporting never smoking in the PAS, IAS and SAS1, respectively.[45] The younger age, as well as the higher proportion of females, Asian patients and never 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.[4, 13, 57]

The median time from diagnosis was [redacted] months for the total population (PAS: [redacted]; IAS: [redacted]; SAS1: [redacted]) (Table 10). Most patients in the PAS ([redacted]) and IAS ([redacted]), and [redacted], had metastatic disease at enrolment, with 36%, [redacted] and 18% exhibiting CNS metastases at baseline in the PAS, IAS and SAS1, respectively. In addition, most patients in the PAS and SAS1 were diagnosed with Stage IV disease ([redacted]). This was higher than England, where 46.8% of NSCLC patients were diagnosed at Stage IV in 2017.[12] NGS on tumour samples ([redacted]) was the most common method of determining *RET* fusion status, which will mirror English clinical practice following the imminent establishment of Genomic Hubs.[45]

In accordance with the eligibility criteria for this population, all patients in the PAS population had received at least 1 prior line of platinum-based chemotherapy and 55.2% had also received prior immunotherapy (Table 11). [redacted] patients in the IAS had received at least 1 prior line of platinum-based chemotherapy and [redacted] had also received prior immunotherapy. These treatments mirror the currently available regimens in use in England in the first line setting.[10] However, 47.6% of patients in the PAS, and [redacted]% of patients in the IAS population, also received MKI therapy. In line with the analysis set eligibility criteria, no patients in SAS1 received prior therapy.

More than half of patients in the PAS and IAS underwent prior radiotherapy ([redacted] and [redacted], respectively) and roughly half had undergone cancer related surgery ([redacted] and [redacted], respectively). For the PAS population, [redacted] ([redacted]) of patients had received 1–2 prior systemic therapies, with a similar value also reported for the IAS population ([redacted] [[redacted]). Notably, only [redacted] of patients in the PAS and [redacted] of IAS patients achieved a partial response with the last systemic therapy received (Table 11).

Table 9. Baseline demographic characteristics for *RET* fusion-positive NSCLC patients

Characteristics	PAS (sub-set of IAS) N = 105	IAS (prior platinum chemo) N = 184	SAS1 (untreated) N = 39	SAS2 (prior other systemic therapy) N = 16	SAS3 (non-measurable disease) N = 14	Total N = 253
Age, years						
Median (range)	61.0 (23–81)	[redacted]	61.0 (23–86)	[redacted]	[redacted]	[redacted]
Overall age group, n (%)						
18–44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45–64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	43 (41.0)	[redacted]	17 (43.6)	[redacted]	[redacted]	[redacted]
Female	62 (59.0)	[redacted]	22 (56.4)	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	55 (52.4)	[redacted]	28 (71.8)	[redacted]	[redacted]	[redacted]
Black	5 (4.8)	[redacted]	3 (7.7)	[redacted]	[redacted]	[redacted]
Asian	40 (38.1)	[redacted]	7 (17.9)	[redacted]	[redacted]	[redacted]
Other/Missing	5 (4.8)	[redacted]	1 (2.6)	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body mass index, kg/m^2						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG, n (%)						
0	31 (29.5)	[redacted]	18 (46.2)	[redacted]	[redacted]	[redacted]
1	72 (68.6)	[redacted]	21 (53.8)	[redacted]	[redacted]	[redacted]
2	2 (1.9)	[redacted]	0	[redacted]	[redacted]	[redacted]
Smoking history, n (%)						
Never smoked	75 (71.4)	[redacted]	29 (74.4)	[redacted]	[redacted]	[redacted]
Former smoker	29 (27.6)	[redacted]	9 (23.1)	[redacted]	[redacted]	[redacted]
Current smoker	1 (1.0)	[redacted]	1 (2.6)	[redacted]	[redacted]	[redacted]
Missing	0	[redacted]	0	[redacted]	[redacted]	[redacted]

Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2 and SAS3.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45] Drilon et al. 2020.[57]

Table 10. Baseline disease characteristics for *RET* fusion-positive NSCLC patients

Characteristics	PAS (sub-set of IAS) N = 105	IAS (prior platinum chemo) N = 184	SAS1 (untreated) N = 39	SAS2 (prior other systemic therapy) N = 16	SAS3 (non-measurable disease) N = 14	Total N = 253
Stage at diagnosis, n (%)						
I, IA, IB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II, IIA, IIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA, IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis, months						
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of metastatic disease, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time from diagnosis of metastatic disease, months						
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least 1 measurable lesion by investigator, n (%)						
Yes	104 (99.0)	[redacted]	39 (100)	[redacted]	[redacted]	[redacted]
No	1 (1.0)	[redacted]	0	[redacted]	[redacted]	[redacted]

Sum of diameters at baseline by investigator, mm						
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNS metastases at baseline by investigator, n (%)						
Yes	38 (36.2)	[redacted]	7 (17.9)	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The "Total" column is the sum of the IAS, SAS1, SAS2 and SAS3.
Abbreviations: CNS: central nervous system; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45] Drilon et al. 2020.[57]

Table 11. Prior cancer-related treatments for *RET* fusion-positive NSCLC

Characteristics	PAS (sub-set of IAS) N = 105	IAS (prior platinum chemo) N = 184	SAS1 (untreated) N = 39	SAS2 (prior other systemic therapy) N = 16	SAS3 (non-measurable disease) N = 14	Total N = 253
Type of prior systemic therapy, n (%)						
Platinum Chemotherapy	105 (100)	[redacted]	0	[redacted]	[redacted]	[redacted]
Anti-PD-1/PD-L1 Therapy	58 (55.2)	[redacted]	0	[redacted]	[redacted]	[redacted]
MKI	50 (47.6)	[redacted]	0	[redacted]	[redacted]	[redacted]
Prior systemic regimens, n (%)						
0	[redacted]	[redacted]	39 (100)	[redacted]	[redacted]	[redacted]
1–2	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Number of prior systemic regimens						
Median (range)	3.0 (1–15)	[redacted]	0	[redacted]	[redacted]	[redacted]
Best response to last systemic treatment, n (%)						
Complete response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior radiotherapy, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer related surgery, n (%)						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2 and SAS3.
Abbreviations: IAS: Integrated Analysis Set; MKI: multi kinase inhibitor; PAS: Primary Analysis Set; PD-L1: programmed death ligand 1; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45] Drilon et al. 2020.[57]

B.2.3.5 Participant flow

The patient disposition of the *RET* fusion-positive NSCLC analysis sets is presented in Table 12. Of the 253 patients with *RET* fusion-positive NSCLC included in the summary of clinical efficacy, [redacted] patients ([redacted]) were still on treatment as of the 16th December 2019 data cut-off.[45]

In the PAS of 105 patients, [redacted] ([redacted]) were still on treatment and [redacted] patients ([redacted]) in the IAS were still on treatment. In the PAS, [redacted] patients ([redacted]) stayed on treatment post progression at the discretion of the investigator.[45] Of the 39 first line patients with *RET* fusion-positive NSCLC (SAS1), [redacted] patients ([redacted]) were still on treatment. For all patients with *RET* fusion-positive NSCLC, the most common reason for treatment discontinuation was disease progression ([redacted]). A similar proportion in the PAS also discontinued for this reason ([redacted]).[45]

Table 12. Patient disposition of *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial as of the December 2019 data cut-off

	PAS (sub-set of IAS)	IAS (prior platinum chemo)	SAS1 (untreated)	SAS2 (prior other systemic therapy)	SAS3 (non-measurable disease)	Total
Treated	105	184	39	16	14	253
Treatment ongoing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment continued post-progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status continuing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study status discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: For *RET* fusion-positive NSCLC, the PAS includes the first 105 patients of the IAS. The Total column is the sum of the IAS, SAS1, SAS2 and SAS3.
Abbreviations: IAS: Integrated analysis set, PAS: Primary Analysis Set; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

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 13. 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 local population. However, because the trial is ongoing, some points were inconclusive.

Table 13. Quality assessment of the LIBRETTO-001 trial

Study ID: LIBRETTO-001	
Reference: Wirth LJ, Cabanillas ME, Sherman E, Solomon B, Leboulleux S, Robinson B, et al. Clinical activity of Loxo-292, a highly selective *RET* inhibitor, in patients with RET-altered thyroid cancers. Thyroid. 2018;28:A171[63]	
Oxnard G, Subbiah V, Park K, Bauer T, Wirth L, Velcheti V, et al. Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with *RET* Fusion+ Non-Small Cell Lung Cancer. Journal of Thoracic Oncology. 2018;13(10):S349-S350[64]	
Wirth L, Sherman E, Drilon A, Solomon B, Robinson B, Lorch J et al. LBA93 Registrational results of LOXO-292 in patients with *RET*-altered thyroid cancers. Ann Oncol, Volume 30, Issue Supplement_5, October 2019[65]	
Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer https://ClinicalTrials.gov/show/NCT03157128[1]	
Study Question	**Grade (yes/no/unclear)**
1. Did the study address a clearly focused issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of LOXO-292 in patients with advanced solid tumours including *RET* fusion-positive solid tumours, MTC, and other tumours with RET activation. This is abstract only so only CT.gov has information on inclusion and exclusion. The primary endpoint is MTD and secondary endpoints include safety, ORR, and DOR
2. Was the cohort recruited in an acceptable way?	Cannot tell. Abstract only but clear inclusion and exclusion criteria outlined on CT.gov. 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 a RECIST assessment and assessed by an IRC. Adverse events were not assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it is an open-label, single-arm study
5A. Have the authors identified all important confounding factors?	Cannot tell. Abstract only

List the ones you think might be important, that the author missed.	
5B. Have they taken account of the confounding factors in the design and/or analysis?	Cannot tell. Abstract only
6A. Was the follow up of subjects complete enough?	Cannot tell. This is an ongoing trial
6B. Was the follow up of subjects long enough?	Cannot tell. This is an ongoing trial
7. What are the results of this study?	LOXO-292 was well-tolerated and had marked antitumor activity in *RET* fusion-positive NSCLC patients, including those with resistance to prior MKIs and brain metastases from the initial results resented
8. How precise are the results?	The results were precise. RECIST assessment was used on all scans to determine the ORR with an IRC. Adverse events will need to be assessed using CTCAE in the future
9. Do you believe the results?	Yes. However, the study is ongoing and abstract only
10. Can the results be applied to the local population?	Yes. These results can be applied to other thyroid cancer and NSCLC patients with *RET*-altered tumours
11. Do the results of this study fit with other available evidence?	Cannot tell. No targeted therapy is approved for patients with RET-altered tumours, but the results are similar to vandetanib which also selectively targets *RET* signalling
12. What are the implications of this study for practice?	The results from this small single-arm study show LOXO-292 as a potential effective therapy for thyroid cancer and NSCLC patients with *RET*-altered tumours

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; 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

- The efficacy of selpercatinib in *RET* fusion-positive NSCLC has been demonstrated in LIBRETTO-001, a first in-human Phase I/II trial[57]
- The primary endpoint used in LIBRETTO-001 was ORR, defined as the proportion of patients with a BOR of confirmed CR or PR based on RECIST v1.1 and IRC assessment:
    - In the **first line** (SAS1) trial population, the **ORR** was 85% (33/39, 95% CI: 69.5–94.1)
    - In the **second line** (PAS) trial population, the **ORR** was 64% (67/105; 95% CI: 53.9–73.0)
    - In the **second line** (IAS) trial population, the **ORR** was [redacted] ([redacted])
    - Across the three trial populations, selpercatinib treatment resulted in high tumour response rates in both first line and second line *RET* fusion-positive NSCLC patients, decreasing tumour size and delaying disease progression for most patients

- DOR was a secondary outcome in LIBRETTO-001:
  - In the **first line** (SAS1) trial population, the **median DOR** was not reached (95% CI: 12.0–not estimable [NE]) at the time of data cut-off, with PD observed in only seven (21%) patients in a median follow-up of 7.4 months
  - In the **second line** (PAS) trial population, the **median DOR** was 17.5 months (95% CI: 12.0–NE), with death or disease progression observed for 23/67 (34%) patients in a median follow-up of 12.1 months
  - In the **second line** (IAS) trial population, the **median DOR** was [redacted] months ([redacted]), with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
  - Across the three trial populations, results indicated that the high response rates observed with selpercatinib administration were durable in a high proportion of first and second line *RET* fusion-positive NSCLC patients, thereby maintaining their HRQoL levels for longer. Preliminary OS estimates suggest good overall survival rates for patients treated with selpercatinib
- PFS was a secondary outcome in LIBRETTO-001:
  - In the **first line** (SAS1) trial population, the **median PFS** by IRC assessment was not reached (95% CI: 13.8–NE), with death or disease progression only reported in 9/39 (23%) patients in a median follow-up of 9.2 months
  - In the **second line** (PAS) trial population, the **median PFS** was 16.5 months (95% CI: 13.7–NE), with death or disease progression observed in 44/105 (42%) patients in a median follow-up of 13.9 months
  - In the **second line** (IAS) trial population, the **median PFS** was [redacted] months ([redacted]), with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
  - Progressed disease is associated with reduced patient HRQoL.[14] Results indicate that selpercatinib treatment could bring positive benefits to first and second line *RET* fusion-positive NSCLC patients, by delaying disease progression and helping patients to maintain their quality of life for longer
- OS was considered as a secondary outcome in LIBRETTO-001:
  - In the **first line** (SAS1) trial population, the **median OS** was [redacted] ([redacted]) at the 16th December 2019 data cut-off, with only [redacted] ([redacted]) death reported in a median follow-up of [redacted] months
  - In the **second line** (PAS) trial population, the **median OS** was [redacted] ([redacted]). Death was observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
  - In the **second line** (IAS) trial population, the **median OS** was [redacted] ([redacted]. Death was observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months
- Patient reported outcomes were assessed using the EORTC QLQ-C30:
  - Patients experienced definite improvements in QLQ-C30 sub scores: physical (n = [redacted] [[redacted]]), emotional (n = [redacted] [[redacted]]), role (n = [redacted] [[redacted]]), cognitive (n = [redacted] [[redacted]]) and social function (n = [redacted] [[redacted]]). There was a median time to definite improvement amongst NSCLC patients of [redacted] months
  - In general, a higher proportion of NSCLC patients reported improved, rather than worsening, QLQ-C30 scores, with [redacted] versus [redacted] of patients reporting improved versus worsened global health status scores during Cycle 9 of selpercatinib treatment

- In line with clinical effectiveness measures, QLQ-C30 scores indicate improved quality of life for advanced *RET* fusion-positive NSCLC patients receiving selpercatinib
- The results of LIBRETTO-001 demonstrate that treatment with selpercatinib results in a high and durable response rate for both first and second line RET fusion-positive NSCLC patients and corresponds with improvements in patient quality of life

The clinical effectiveness of selpercatinib in NSCLC was demonstrated in LIBRETTO-001, a first in-human Phase I/II trial.[57] The clinical effectiveness results from this trial, assessed by IRC, are summarised under the relevant primary and secondary endpoints for this submission and for each study population (first line: SAS1 and second line: PAS and IAS). Results from the Investigator assessment are available in Appendix L. EORTC data for NSCLC patients completing a baseline assessment (N = [redacted]) is summarised at the end of the section, although data are not divided by treatment history.

B.2.5.1 First line population (SAS1)

The SAS1 population was comprised of patients with *RET* fusion-positive NSCLC who had not received prior systemic therapy (N = 39) (see Table 6, Section B.2.3.3 for further details).[45] This analysis set provides evidence for the efficacy of selpercatinib in first line patients with advanced *RET* fusion-positive NSCLC. As of the 16th December 2019 data cut-off, all 39 patients had at least 6 months follow-up from the first dose of selpercatinib.[45]

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 8, Section B.2.3.3). For first line patients with *RET* fusion-positive NSCLC, the ORR was 85% (33/39, 95% CI: 69.5–94.1) by IRC assessment (Table 14). Based on BOR, [redacted] of previously untreated patients were assessed to have stable disease, whilst the majority were assessed to have a partial response (84.6%). Only 1 patient (2.6%) was assessed to have progressive disease.[45]

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 7, demonstrating that at the data cut-off, tumour diameter had decreased in all of the 39 patients, decreasing by more than 30% (i.e. a partial response was achieved) in all but 3 patients.[45] Results indicate that selpercatinib treatment results in high response rates in previously untreated *RET* fusion-positive NSCLC patients, preventing disease progression and decreasing tumour size for the majority of patients.

Table 14. BOR and ORR for first line *RET* fusion-positive NSCLC patients

	First line (SAS1) N = 39
Best overall response, n (%)	
Complete response	0
Partial response	33 (84.6)
Stable disease	4 (10.3)
Progressive disease	1 (2.6)

Not evaluable	1 (2.6)
Objective response rate (CR + PR)	
n (%)	33 (84.6)
95% CI	[redacted]

Abbreviations: CI: confidence intervals; CR: complete response; PR: partial response; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45] Drilon et al. 2020.[57]

Figure 7. Waterfall plot of best change in tumour burden based on IRC assessment for first line *RET* fusion-positive NSCLC patients

[redacted]

Note: 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: NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

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 7 (Section B.2.3.3).

Of the 33 first line *RET* fusion-positive NSCLC patients who responded to treatment with selpercatinib, at the data cut-off, the majority [redacted] were alive with no documented disease progression. The median DOR by IRC assessment was not reached (95% CI: 12.0–NE) at the time of data cut-off for these patients, with PD observed in only [redacted] ([redacted]) patients in a median follow-up of 7.4 months (Table 15). As of the 16th December 2019 data cut-off, [redacted] ([redacted]) patients had maintained a response for ≥12 months.[45]

By Kaplan-Meier estimate, the probability of remaining in response at 6 months was [redacted] ([redacted]) and [redacted] ([redacted]) at 12 months.[45] These results indicated that patient benefit from a decrease in tumour size was durable, with almost all first line 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 physical and physiological benefit to patients, which also translated into stable or improved quality of life (see Section B.2.5.3). The Kaplan-Meier plot of DOR is presented in Figure 8.[45]

Table 15. DOR for first line *RET* fusion-positive NSCLC patients

	Responders at first line (SAS1) (N = [redacted])
Response status n (%)	
Disease progression	[redacted]
Censored	26 (78.8)
Reason censored n (%)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without document PD	[redacted]
DOR (months)	
Median	NE
95% CI	12.0–NE
Minimum–maximum	[redacted]
Rate (%) of DOR	
6 months or more	[redacted]
95% CI	[redacted]
12 months or more	[redacted]
95% CI	[redacted]
DOR follow-up (months)	
Median	7.39
25th, 75th percentiles	[redacted]
Observed DOR n (%)[a]	
<6 months	[redacted]
≥6 to 12 months	[redacted]

	Responders at first line (SAS1) (N = [redacted])
≥12 to 18 months	[redacted]
≥18 to 24 months	[redacted]
≥24 months	[redacted]

Footnotes: [a]Includes censored patients who have not yet progressed.
Notes: Censored observations denoted by "+".
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 (16th December 2019 cut-off);[45] Drilon et al. 2020.[57]

Figure 8. Kaplan-Meier plot of DOR based on IRC assessment for first line *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by "+".
Abbreviations: DOR: duration of response.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Secondary endpoint: Progression free survival

For assessment of PFS, an event was recorded for death of a patient before the first planned visit or death or disease progression in a patient between planned disease assessments. Patients were censored as per the criteria listed in Table 7 (Section B.2.3.3).

All first line *RET* fusion-positive NSCLC patients were followed for at least [redacted] months from first dose. As of the December 16th data cut-off, the majority ([redacted]) of patients were alive and without documented PD. The median PFS by IRC was not reached (95% CI: 13.8–NE), with death or disease progression only reported in [redacted] ([redacted]) patients in a median follow-up of 9.2 months (Table 16).[45] [redacted] ([redacted]) patients were progression free for ≥12 months, as of the December 2019 data cut-off.[45]

By Kaplan-Meier estimate, the probability of being progression-free at 6- and 12- months was [redacted] ([redacted]) and [redacted] ([redacted]), respectively, by IRC assessment.[45] These results indicate that administration of selpercatinib can produce clinically meaningful responses for a high proportion of untreated patients, with three-quarters 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 could bring positive benefits to first line *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their quality of life for longer periods of time.[14] The Kaplan-Meier plot of PFS is presented in Figure 9.[45]

Table 16. PFS for first line *RET* fusion-positive NSCLC patients

	First line (SAS1) N = 39
Progression status n (%)	
Disease progression	[redacted]
Died (no disease progression beforehand)	[redacted]
Censored	30 (76.9)
Reason censored (n, %)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without document PD	[redacted]
Duration of PFS (months)	
Median	NE
95% CI	13.8–NE
Minimum–maximum	[redacted]
Rate (%) of PFS	
6 months or more	[redacted]
95% CI	[redacted]
12 months or more	[redacted]
95% CI	[redacted]
Duration of follow-up (months)	
Median	9.17
25th, 75th percentiles	[redacted]

	First line (SAS1) N = 39
Observed duration of PFS n (%)[a]	
<6 months	[redacted]
≥6 to 12 months	[redacted]
≥12 to 18 months	[redacted]
≥18 months	[redacted]

Footnotes: [a]Includes censored patients who have not yet progressed.
Notes: Censored observations denoted by "+".
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 (16th December 2019 cut-off);[45] Drilon et al. 2020.[57]

Figure 9. Kaplan-Meier plot of PFS based on IRC assessment for first line *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by "+".
Abbreviations: PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

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 7, Section B.2.3.3). The censoring date was determined from the date the patient was last known to be alive.

The median OS was [redacted] ([redacted]) for first line *RET* fusion-positive NSCLC patients at the 16th December 2019 data cut-off, with only [redacted] ([redacted]) death reported in a median follow-up of [redacted] months. At 12 months, the Kaplan-Meier predicted OS rate was [redacted] ([redacted]), providing preliminary evidence to support the use of selpercatinib for the prolongation of life (Table 17).[45] No Kaplan-Meier plot is presented, due to the low number of events.

Table 17. OS for first line *RET* fusion-positive NSCLC patients

	First line (SAS1) N = 39
Survival status n (%)	
Dead	[redacted]
Alive	[redacted]
Duration of OS (months)	
Median	[redacted]
95% CI	[redacted]
Minimum–maximum	[redacted]
Rate (%) of OS	
12 months or more	[redacted]
95% CI	[redacted]
Duration of follow-up (months)	
Median	[redacted]
25th, 75th percentiles	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: CI: confidence intervals; NE: not evaluable; OS: overall survival; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

B.2.5.2 Second line subpopulation (PAS and IAS)

The PAS population was comprised of patients with *RET* fusion-positive NSCLC, who had received ≥1 lines of prior platinum-based chemotherapy and who completed at least 6 months of follow-up (N = 105) and was a subset of the IAS, which was comprised of 184 pre-treated *RET* fusion-positive patients (see Section B.2.3.3 for further details of both analysis sets).[57] Both analysis sets provide evidence for the efficacy of selpercatinib in the second line setting in patients with advanced *RET* fusion-positive NSCLC.[57]

Primary endpoint: Objective response rate

The ORR, defined as the proportion of patients with BOR of confirmed CR or PR based on RECIST v1.1, was 64% (67/105; 95% CI: 53.9–73.0) by IRC assessment for the PAS and [redacted] ([redacted]) for the IAS population at the 16th December 2019 data cut-off (Table 18). In the PAS population, the majority (65; 61.9%) of patients achieved a PR, whilst two (1.9%)

patients achieved a CR, 30 (28.6%) were assessed to have SD, while only 4 (3.8%) patients were assessed as having PD at the 16th December 2019 data cut-off.[57] A similar response to selpercatinib was observed in IAS patients, with the majority ([redacted]; [redacted]) achieving a PR and [redacted] ([redacted]) achieving a CR, while stable disease was reported for [redacted]) patients and PD was reported for only [redacted] ([redacted]) patients.

Waterfall plots Figure 10 and Figure 11 illustrate the best overall change in tumour size, as per RECIST v1.1, for both second line analysis sets at the 16th December 2019 data cut-off.[45] These demonstrate that an increase in tumour diameter of ≥20% from baseline (PD) was reported in a very small proportion of patients ([redacted] in the PAS and [redacted] in the IAS), while the majority of patients in both populations achieved a decrease in tumour diameter of ≥30% from baseline (PR).[45]

Overall, these results indicate that selpercatinib treatment results in high response rates, even amongst second line *RET* fusion-positive NSCLC patents, preventing disease progression and thereby maintaining patients' HRQoL.

Table 18. BOR and ORR for second line (PAS and IAS) *RET* fusion-positive NSCLC patients

	Second line (PAS) N = 105	Second line (IAS) N = 184
Best overall response, n (%)		
Complete response	2 (1.9)	[redacted]
Partial response	65 (61.9)	[redacted]
Stable disease	30 (28.6)	[redacted]
Progressive disease	4 (3.8)	[redacted]
Not evaluable	4 (3.8)	[redacted]
Objective response rate (CR+PR)		
n (%)	67 (63.8)	[redacted]
95% CI	[redacted]	[redacted]

Note: PAS includes 4 patients with non-measurable disease per IRC.
Abbreviations: CI: confidence intervals; CR: complete response; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; PR: partial response.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45] Drilon et al. 2020.[57]

Figure 10. Waterfall plot of best change in tumour size based on IRC assessment for second line (PAS) *RET* fusion-positive NSCLC patients

[redacted]

Note: 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: CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Figure 11. Waterfall plot of best change in tumour size based on IRC assessment for second line (IAS) *RET* fusion-positive NSCLC patients

[redacted]

Note 1: 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.
Note 2: Fourteen patients are not shown due to 10 patients having non-target lesions only, and 4 patients with no post-baseline target lesion measurements.
Abbreviations: CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Secondary endpoint: Duration of response

For assessment of DOR, an event was recorded for death or disease progression in a patient. Patients were censored as per the criteria listed in Table 7 (Section B.2.3.3).

As of the 16th December 2019 data cut-off, the majority of patients who responded to selpercatinib treatment in both the PAS ([redacted]) and the IAS ([redacted]) populations were alive and without disease progression, as assessed by IRC. In the PAS population, the median DOR by IRC was 17.5 months (95% CI: 12.0–NE), with death or disease progression observed for [redacted] ([redacted]) patients in a median follow-up of 12.1 months. For the IAS population the median DOR was [redacted] months ([redacted]), with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months. [redacted] ([redacted]) patients have been in response for ≥12 months in both analysis sets, as of the December 2019 data cut-off (Table 19).[45]

By Kaplan-Meier estimate, the probability of remaining in response at 6- and 12- months was [redacted] ([redacted]) and [redacted] ([redacted]), respectively for the PAS. Similar results were reported from the broader IAS population ([redacted]; 95% CI: [redacted] and [redacted]; 95% CI: [redacted], respectively). The Kaplan-Meier plot of DOR for the PAS and IAS are presented in Figure 12 and Figure 13, respectively.

Overall, these results indicate that the high response rates observed with selpercatinib administration were durable in a high proportion of second line *RET* fusion-positive NSCLC patients, allowing them to remain progression free for longer and thereby prolonging patients' HRQoL levels.[45]

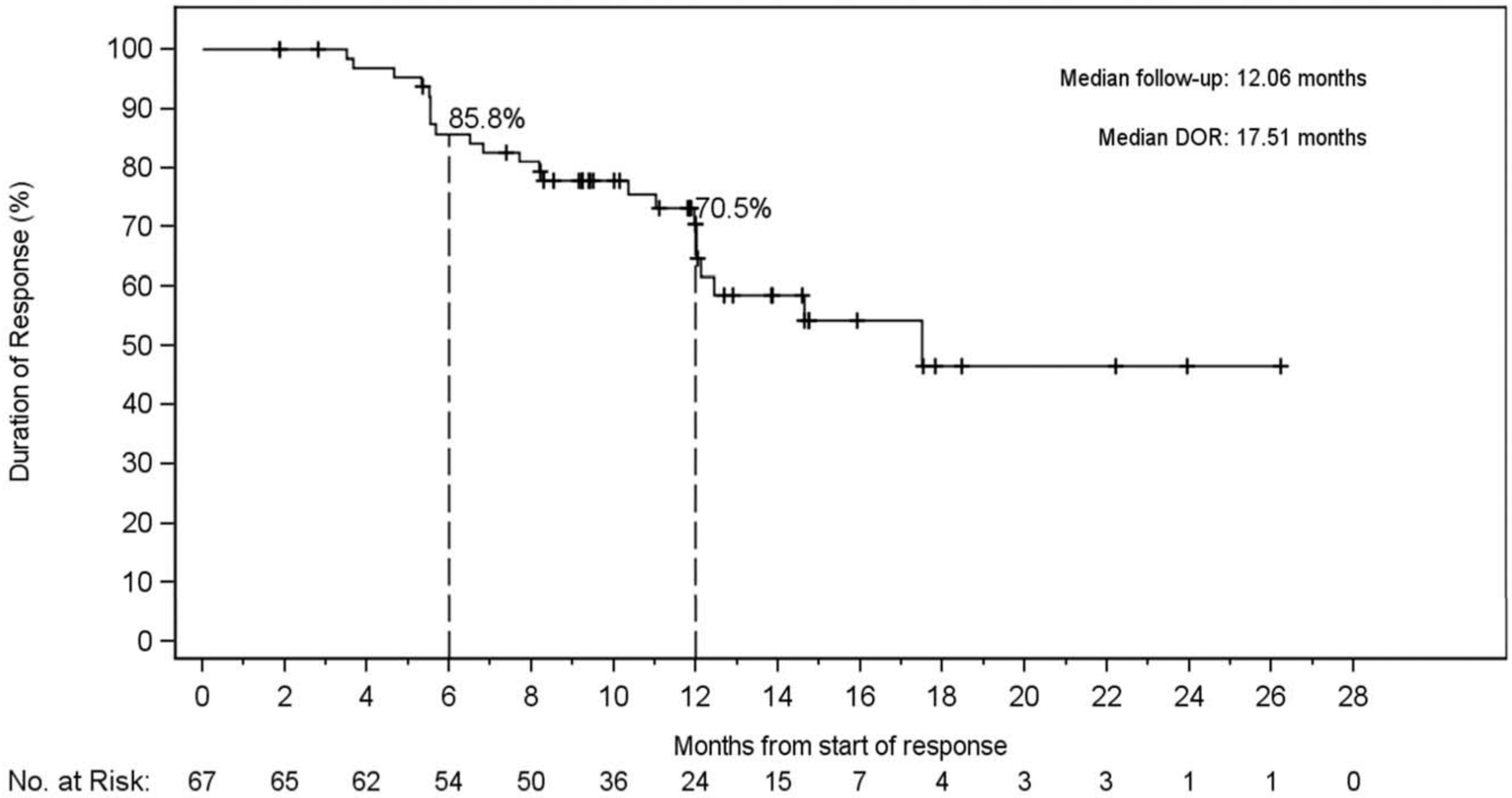
Table 19. DOR for second line (PAS and IAS) *RET* fusion-positive NSCLC patients

	Responders at second line (PAS) N = [redacted]	Responders at second line (IAS) N = [redacted]
Response status, n (%)		
Disease progression	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]
Censored	44 (65.7)	[redacted]
Reason censored, n (%)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented disease progression	[redacted]	[redacted]
Discontinued from study without documented disease progression	[redacted]	[redacted]
DOR (months)		
Median	17.51	[redacted]
95% CI	12.0–NE	[redacted]
Minimum–maximum	[redacted]	[redacted]
Rate (%) of DOR		
6 months or more	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
12 months or more	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

DOR follow-up (months)		
Median	12.06	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Observed DOR, n (%)[a]		
<6 months	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]

Footnotes: [a]Includes censored patients who have not yet progressed.
Notes: Censored observations denoted by "+".
Abbreviations: CI: confidence intervals; DOR: duration of response; IAS: Integrated Analysis Set; NE: not evaluable; PAS: Primary Analysis Set.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45] Drilon et al. 2020.[57]

Figure 12. Kaplan-Meier plot of DOR based on IRC assessment for second line (PAS) *RET* fusion-positive NSCLC patients



Note: Censored patients denoted by "+".
Abbreviations: DOR: duration of response.
Source: Drilon et al. 2020, Supplementary Appendix.[66]

Figure 13. Kaplan-Meier plot of DOR based on IRC assessment for second line (IAS) *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by "+".
Abbreviations: DOR: duration of response.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Secondary endpoint: Progression free survival

For assessment of PFS, an event was recorded for the death of a patient before the first planned visit or death or disease progression of a patient between planned disease assessments. Patients were censored as per the criteria listed in Table 7 (Section B.2.3.3).

As of the 16th December 2019 data cut-off, [redacted] patients in the PAS and [redacted]) IAS patients were alive and without disease progression, by IRC assessment (Table 20).[45] The median PFS was 16.5 months (95% CI: 13.7–NE) in the PAS, with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of 13.9 months.[57] The median PFS for the IAS was slightly longer at [redacted] months ([redacted]), with death or disease progression observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months. [redacted] ([redacted]) patients in the PAS and [redacted] ([redacted]) patients in the IAS were progression-free for ≥12 months, as of the 16th December 2019 data cut-off.[45]

By Kaplan-Meier estimate, the probability of being progression-free at 6- and 12- months was [redacted] ([redacted]) and [redacted] ([redacted]), respectively for the PAS population.[45] Similar results were observed in the IAS population ([redacted]; 95% CI: [redacted] and [redacted]; 95% CI: [redacted], respectively). These predictions should be considered alongside the result that [redacted] of PAS and [redacted] of IAS patients had experienced disease progression as their best response to prior systemic treatment (see Table 11, Section B.2.3.4). The Kaplan-Meier plots of PFS for the PAS and IAS populations are presented in Figure 14 and Figure 15, respectively.[45]

These results indicate that treatment with selpercatinib will allow second line *RET* fusion-positive NSCLC to remain progression-free for an extended period, thereby increasing patients' HRQoL.[14]

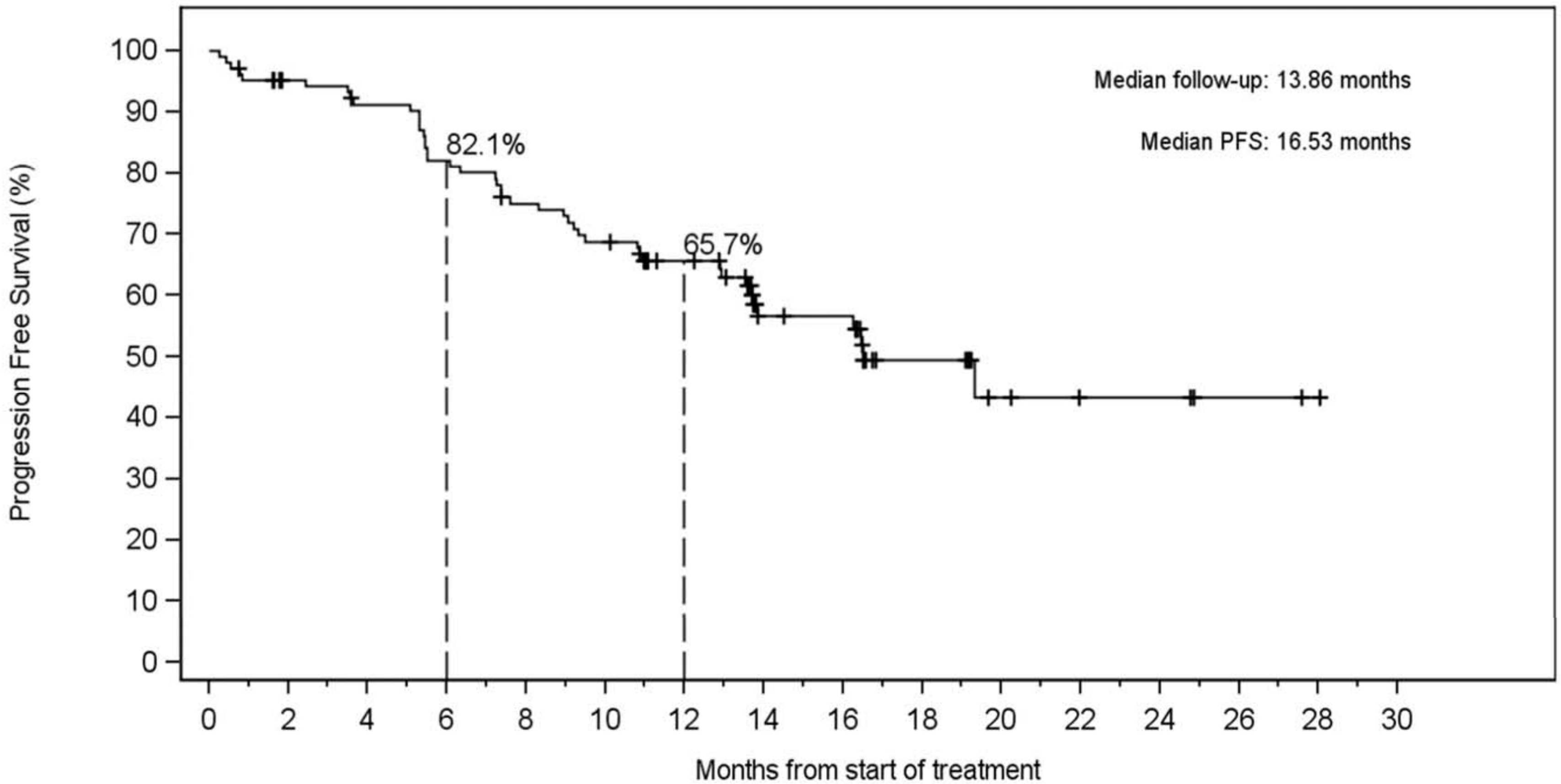
Table 20. PFS for second line (PAS and IAS) *RET* fusion-positive NSCLC patients

	Second line (PAS) N = 105	Second line (IAS) N = 184
Progression status n (%)		
Disease progression	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]
Censored	61 (58.1)	[redacted]
Reason censored n (%)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer related surgery without documented disease progression	[redacted]	[redacted]
Discontinued from study without documented disease progression	[redacted]	[redacted]
Duration of PFS (months)		
Median	16.53	[redacted]
95% CI	13.7–NE	[redacted]
Minimum–maximum	[redacted]	[redacted]
Rate (%) of PFS		
≥6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

≥12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Duration of follow-up (months)		
Median	13.86	[redacted]
25th, 75th percentiles	[redacted]	[redacted]
Observed duration of PFS n (%)[a]		
<6 months	[redacted]	[redacted]
≥6 to 12 months	[redacted]	[redacted]
≥12 to 18 months	[redacted]	[redacted]
≥18 to 24 months	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]
Progression status n (%)		
Disease progression	[redacted]	[redacted]
Died (no disease progression beforehand)	[redacted]	[redacted]
Censored	[redacted]	[redacted]

Footnotes: [a]Includes censored patients who have not yet progressed.
Notes: Censored observations denoted by "+".
Abbreviations: CI: confidence intervals; NE: not evaluable; IAS: Integrated Analysis Set; PAS: Primary Analysis Set; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45]Drilon et al. 2020.[57]

Figure 14. Kaplan-Meier plot of PFS based on IRC assessment for second line (PAS) *RET* fusion-positive NSCLC patients



No. at Risk:	105	95	90	81	73	67	51	29	28	13	6	4	4	2	1	0

Note: Censored patients denoted by "+".
Abbreviations: PFS: progression free survival.
Source: Drilon et al. 2020, Supplementary Appendix.[66]

Figure 15. Kaplan-Meier plot of PFS based on IRC assessment for second line (IAS) *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by “+”.
Abbreviations: PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Secondary endpoint: Overall survival

The median OS was not reached for either the PAS ([redacted]) nor the IAS ([redacted] populations.[45] As of the 16th December 2019 data cut-off, the majority of patients were alive in both the PAS ([redacted] and IAS ([redacted]) populations. In the PAS population, death was observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months, whilst in the IAS population, death was observed in [redacted] ([redacted]) patients in a median follow-up of [redacted] months (Table 21). At 12 months, the Kaplan-Meier predicted OS rate was [redacted] ([redacted]) and [redacted] ([redacted]for the PAS and IAS, respectively.[45] The Kaplan-Meier plot of OS for the PAS and IAS is shown in Figure 16 and Figure 17, respectively. Although OS data remains immature, preliminary results suggest that selpercatinib treatment may offer survival benefits to second line patients with advanced *RET* fusion-positive NSCLC.

Table 21. OS for second line (PAS) *RET* fusion-positive NSCLC patients

	Second line (PAS) N = 105	Second line (IAS) N = 184
Survival status, n (%)		
Dead	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Duration of OS (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Minimum–maximum	[redacted]	[redacted]
Rate (%) of OS		
12 months or more	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Duration of follow-up (months)		
Median	[redacted]	[redacted]
25th, 75th percentiles	[redacted]	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: CI: confidence interval; NE: not estimable; OS: overall survival; PAS: Primary Analysis Set.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Figure 16. Kaplan-Meier plot of OS for second line (PAS) *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by "+".
Abbreviations: OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Figure 17. Kaplan-Meier plot of OS for second line (IAS) *RET* fusion-positive NSCLC patients

[redacted]

Note: Censored patients denoted by "ǀ".
Abbreviations: OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

B.2.5.3 EORTC QLQ-C30

As of the 16th December 2019 data cut-off, [redacted] patients with *RET* fusion-positive NSCLC had completed a baseline assessment as part of a "QLQ-C30 Analysis Set". EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks until the end of treatment visit (see Table 8, Section B.2.3.3 for further details of EORTC QLQ-C30 methodology).[45]

The mean baseline score for global health status/QoL subscale was [redacted] (standard deviation [SD]: [redacted]). Of the [redacted] patients, [redacted] experienced definite improvement in the global health status/QoL subscale. Of those with definite improvement, there was a median time to definite improvement of [redacted] months. The average scores for the physical, emotional, role, cognitive and social functioning subscales were each [redacted] points at baseline.[45]

NSCLC patients (N = [redacted]) reported mean (SD) baseline scores for QLQ-C30 subscales of [redacted]) for physical functioning; [redacted]) for emotional functioning; [redacted]) for role functioning; [redacted]) for cognitive functioning and [redacted]) for social functioning. Of these [redacted] patients, the proportion who experienced definite improvements in each of the QLQ-C30 subscales as of the data cut-off was [redacted] for physical functioning; [redacted] for emotional functioning; [redacted] for role functioning; [redacted] for cognitive functioning and [redacted] for social functioning. The proportion of patients experiencing definite worsening in QLQ-C30 subscales was [redacted] for physical functioning; [redacted] for emotional functioning; [redacted] for role functioning; [redacted] for cognitive functioning and [redacted] for social functioning. There were no consistent clinically meaningful differences in mean patient scores over time. The proportion of patients with any clinically meaningful improvement or worsening is reported in Table 22 by cycle.[45]

NSCLC patients (N = [redacted]) reported mean (SD) baseline scores for QLQ-C30 symptomology and financial impact subscales of [redacted] ([redacted]) for nausea and vomiting, [redacted] ([redacted]) for fatigue, [redacted] ([redacted] for pain, [redacted] ([redacted]) for dyspnoea, [redacted] ([redacted]) for insomnia, [redacted] ([redacted] for appetite loss, [redacted] ([redacted] for constipation, [redacted] ([redacted] for diarrhoea and [redacted] ([redacted] for financial difficulties. Of these [redacted] patients, the proportion who experienced definite improvements in each of the QLQ-C30 symptoms/financial subscales were [redacted] nausea and vomiting, [redacted] fatigue, [redacted] pain, [redacted] dyspnoea, [redacted] insomnia, [redacted] appetite loss, [redacted] constipation, [redacted] diarrhoea and [redacted] financial difficulties. The proportion of patients experiencing definite worsening in QLQ-C30 symptoms/financial scales was [redacted] nausea and vomiting, [redacted] fatigue, [redacted] pain, [redacted] dyspnoea, [redacted] insomnia, [redacted] appetite loss, [redacted] constipation, [redacted] diarrhoea and [redacted] 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 22). Overall, at the data cut-off the majority of advanced *RET* fusion-positive NSCLC patients had stable or improved quality of life as determined by QLQ-C30 subscales following treatment with selpercatinib.[45]

Table 22. 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
Global health status/QoL	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Physical functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	51 (32.1)	47 (35.1)	37 (33.6)	26 (37.7)
	Worsened	20 (12.6)	16 (11.9)	13 (11.8)	4 (5.8)
Emotional functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	44 (28.2)	38 (29.0)	31 (28.4)	19 (28.4)
	Worsened	21 (13.5)	9 (6.9)	14 (12.8)	9 (13.4)
Role functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	61 (38.4)	52 (38.8)	48 (43.6)	29 (42.0)
	Worsened	40 (25.2)	26 (19.4)	20 (18.2)	14 (20.3)
Cognitive functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	32 (20.5)	27 (20.6)	21 (19.3)	9 (13.4)
	Worsened	37 (23.7)	30 (22.9)	22 (20.2)	19 (28.4)
Social functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	62 (39.7)	61 (46.6)	46 (42.2)	27 (40.3)
	Worsened	27 (17.3)	22 (16.8)	18 (16.5)	14 (20.9)
Nausea and vomiting	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	43 (27.0)	34 (25.4)	31 (28.2)	20 (29.0)
	Worsened	12 (7.5)	12 (9.0)	8 (7.3)	5 (7.2)
Fatigue	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	71 (44.9)	67 (50.0)	53 (48.2)	33 (47.8)
	Worsened	39 (24.7)	26 (19.4)	25 (22.7)	18 (26.1)
Pain	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	73 (45.9)	64 (47.8)	53 (48.2)	26 (37.7)
	Worsened	25 (15.7)	16 (11.9)	12 (10.9)	10 (14.5)
Dyspnoea	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	57 (36.3)	54 (40.6)	43 (39.1)	30 (43.5)
	Worsened	12 (7.6)	12 (9.0)	6 (5.5)	2 (2.9)
Insomnia	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	38 (23.9)	39 (29.1)	33 (30.0)	19 (27.5)
	Worsened	33 (20.8)	20 (14.9)	19 (17.3)	9 (13.0)
Appetite loss	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	54 (34.0)	49 (36.6)	44 (40.4)	27 (39.1)
	Worsened	19 (11.9)	13 (9.7)	15 (13.8)	9 (13.0)
Constipation	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	33 (20.8)	31 (23.1)	24 (21.8)	8 (11.6)
	Worsened	49 (30.8)	29 (21.6)	26 (23.6)	10 (14.5)
Diarrhoea	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	17 (10.9)	10 (7.6)	12 (11.0)	7 (10.4)
	Worsened	31 (19.9)	45 (34.4)	34 (31.2)	15 (22.4)
Financial difficulties	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	36 (23.1)	23 (17.6)	24 (22.0)	11 (16.4)
	Worsened	13 (8.3)	13 (9.9)	12 (11.0)	10 (14.9)

Abbreviations: EORTC QLQ: European Platform of Cancer Research Quality of Life Questionnaire.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

B.2.6 *Subgroup analysis*

The robustness and consistency of the primary analysis was confirmed by pre-specified subgroup analyses. Response rate and duration of response were analysed by several demographic variables using IRC assessment for PAS patients. Subgroup analyses were not performed in the IAS and SAS1 population.[45] The ORR and DOR by other baseline disease characteristics are presented in Table 23.

In patients with ECOG of 0, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months, whilst patients with an ECOG of 1–2 reported an ORR and DOR of [redacted] ([redacted]) and [redacted] months, respectively.[45] In patients who never smoked, the ORR was [redacted] ([redacted]) and the DOR was not reached.[45] In patients who had smoked, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. Women had a higher ORR than men ([redacted] versus [redacted]), although the underpinning cause of this minor efficacy differential was unclear.[45]

In patients who had CNS metastasis at baseline by Investigator assessment, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months.[45] In patients who did not have CNS metastasis, the ORR was [redacted] ([redacted]) and the DOR was not reached. The ORR and DOR for patients with no metastasis at baseline were difficult to characterise due to the low number of patients.[45] Subgroup analysis confirmed that the beneficial results of selpercatinib treatment, in terms of a reduction in tumour size, were broadly consistent across age, gender, race and smoking status.

Table 23. ORR and DOR by demographics for *RET* fusion-positive NSCLC patients (PAS) based on IRC assessment

	N	Responders	ORR% (95% CI)	DOR (Range)
Overall	105	67	[redacted]	[redacted]
Age				
<65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]
1-2	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status				
Never smoked	[redacted]	[redacted]	[redacted]	[redacted]
Smoker	[redacted]	[redacted]	[redacted]	[redacted]

Any metastatic disease				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
CNS metastasis at baseline by investigator				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: CNS: central nervous system; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; NR: not reached; ORR: objective response rate; PR: partial response.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

The ORR and DOR by gene fusion partner are presented in Table 24. In patients with a *KIF5B-RET* fusion, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. In patients with a *CCDC6-RET* fusion, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months.[45] The ORR and DOR for patients with other fusion partners were difficult to characterise due to the low number of patients.[45] In patients where the *RET* fusion partner was unknown (i.e. the molecular test reported a *RET* fusion but did not specify the fusion partner), the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. Subgroup analysis confirmed that ORR to selpercatinib treatment was broadly consistent across different *RET* fusion partners.[45]

The ORR and DOR by type of molecular test are also presented in Table 24. In patients tested with NGS on tumour tissue, the ORR was [redacted] ([redacted]) and the DOR was not reached. In patients tested with NGS on blood/plasma, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. This analysis confirmed that ORR results were consistent despite the type of molecular assay used.[45]

Table 24. ORR and DOR by *RET* fusion partner and type of molecular assay for *RET* fusion-positive NSCLC patients (PAS) based on IRC assessment

	N	Responders	ORR% (95% CI)	DOR (Range)
Overall	105	[redacted]	[redacted]	[redacted]
***RET* fusion partner**				
KIF5B	[redacted]	[redacted]	[redacted]	[redacted]
CCDC6	[redacted]	[redacted]	[redacted]	[redacted]
NCOA4	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
KIAA1468	[redacted]	[redacted]	[redacted]	[redacted]
ARHGAP12	[redacted]	[redacted]	[redacted]	[redacted]
CCDC88C	[redacted]	[redacted]	[redacted]	[redacted]
CLIP1	[redacted]	[redacted]	[redacted]	[redacted]
PRKAR1A	[redacted]	[redacted]	[redacted]	[redacted]
RBPM and DOCK1	[redacted]	[redacted]	[redacted]	[redacted]
TRIM24	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Type of molecular assay				
NGS on blood or plasma	[redacted]	[redacted]	[redacted]	[redacted]

NGS on tumour	[redacted]	[redacted]	[redacted]	[redacted]
PCR	[redacted]	[redacted]	[redacted]	[redacted]
FISH	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: DOR: duration of response; FISH: fluorescence in situ hybridisation; NA: not applicable; NE: not estimable; NGS: next generation sequencing; NR: not reached; PCR: polymerase chain reaction; PR: partial response; ORR: objective response rate, SD; stable disease.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

The ORR and DOR by number of prior therapies received, and type of prior therapy, are presented in Table 25. In patients with 1–2 prior therapies, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. In patients with 3 or more therapies, the ORR was [redacted] ([redacted]) and the DOR was not reached. Efficacy outcomes were therefore broadly consistent across the two subpopulations, with a slightly higher ORR in the patients who had received a greater number of prior therapies.[45]

In patients that had prior anti-PD-1/PD-L1 therapy, the ORR was [redacted] ([redacted]) and the DOR was not reached. In patients that did not receive prior anti-PD-1/PD-L1 therapy, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. In patients that received prior MKI therapy, the ORR was [redacted] ([redacted]) and the DOR was not reached. In patients that did not receive prior MKI therapy, the ORR was [redacted] ([redacted]) and the DOR was [redacted] months. These subgroup analyses confirmed consistent efficacy results in terms of the primary trial outcome (i.e. ORR), regardless of whether a patient did or did not received immunotherapy or MKI treatment.[45] A strong response was maintained in patients who had previously received immunotherapies, which are used frequently on the NHS (as per Lilly market share data).[19]

Table 25. ORR and DOR by number and type of prior therapy for *RET* fusion-positive NSCLC patients (PAS) based on IRC assessment

	N	Responders	ORR% (95% CI)	DOR (Range)
Overall	105	67	[redacted]	[redacted]
Number of prior therapies				
1–2	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-PD-1/PD-L1 therapy				
Yes	58	38	65.5 (51.9–77.5)	[redacted]
No	47	29	61.7 (46.4–75.5)	[redacted]
Prior multi-kinase inhibitor				
Yes	50	32	64.0 (49.2–77.1)	[redacted]
No	55	35	63.6 (49.6–76.2)	[redacted]

Notes: Censored observations denoted by "+".
Abbreviations: DOR: duration of response; NR: not reached; PD-L1: programmed death ligand 1; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45] Drilon et al. 2020, Supplementary Appendix.[66]

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

- 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. An indirect treatment comparison was therefore necessary to compare selpercatinib to other first and second line treatments that were relevant to the decision problem
- A network meta-analysis (NMA) was performed in both the first line and second line NSCLC treatment setting. In order to connect the selpercatinib first and second line treatment arms of LIBRETTO-001 to their respective NMAs, it was necessary to generate a pseudo-control arm. Individual patient data (IPD) from KEYNOTE-189 was used to generate a control arm in the first line setting and IPD from REVEL was used to generate a control arm in the second line setting. Control arm data from both trials were adjusted for the effect of having *RET* fusion-positive status and other prognostic characteristics on survival outcomes using data from the Flatiron Clinico-Genomic database (CGDB) and performing the doubly-robust survival targeted minimum loss-based estimation (TMLE) method

First line treatment

- In the first line treatment setting, ORR, PFS and OS were modelled. Both random effects (RE) and fixed effects (FE) models were assessed for all outcomes
- Results of the RE model are reported for **ORR** in the first line setting for the overall population
  - Selpercatinib demonstrated the highest odds of inducing a tumour response (**ORR**) compared to pemetrexed plus platinum chemotherapy (odds ratio [OR]: [redacted]; 95% credible intervals [CrI]: [redacted]) of all treatments included in the analysis
  - For the subgroup analysis of pembrolizumab monotherapy in patients with PD-L1≥50%, the FE model was used due to poor convergence of the RE model
- Results for a RE model with informative prior results are presented for the first line treatment setting for both **PFS and OS**:
  - Selpercatinib demonstrated the lowest risk of disease progression (**PFS**) compared to pemetrexed plus platinum chemotherapy (hazard ratio [HR]: [redacted]; [redacted]) of all treatments included in the analysis
  - Selpercatinib demonstrated the lowest risk of death (**OS**) compared to pemetrexed plus platinum chemotherapy (HR: [redacted]; 95% CrI: [redacted]) of all treatments included in the analysis

Second line treatment

- In the second line treatment setting, ORR, PFS and OS were modelled. A hierarchical exchange model was used to take account the PD-L1 as a class in the model. Age was significant and included in the model; the results were centred on 61 years of age (the mean age of the second line NSCLC population in LIBRETTO-001). The results for the second line setting are presented below:
  - Selpercatinib demonstrated the highest odds of inducing a tumour response (**ORR**) compared to docetaxel (OR: [redacted]; 95% CrI: [redacted])
  - Selpercatinib demonstrated the lowest risk of disease progression (**PFS**) compared to docetaxel (HR: [redacted] 95% CrI: [redacted] of all treatments included in the analysis
  - Selpercatinib demonstrated the lowest risk of death (**OS**) compared to docetaxel HR: [redacted] 95% CrI: [redacted] of all treatments included in the analysis

Uncertainties in the indirect treatment comparisons

- The process of generating pseudo-comparator arms to connect selpercatinib to the first and second line NMAs was likely to be associated with inherent uncertainty. However, both pseudo-control arms from the KEYNOTE-189 and REVEL trials were adjusted for *RET*-status and other prognostic factors using Flatiron data and the doubly robust, TMLE method. It was not possible to adjust the remainder of the first and second line networks in the same way and instead the HRs estimated from the first and second line NMAs were applied to the pseudo-control arms of KEYNOTE-189 and REVEL to estimate the treatment effect for relevant comparators for selpercatinib
- Further, TMLE-adjustment for additional prognostic factors may have overestimated the treatment effect for pseudo-control arms to connect the first and second line NMAs compared to adjusting for RET-fusion alone by applying the time-acceleration factor. This was more evident for the second line pseudo-control arm where the relative difference reduces dramatically compared to the same adjusted selpercatinib arms
- For seven first line studies informing the PFS network and three studies informing the OS network, there was evidence that the proportional hazards assumption may not have held. Most studies did not violate proportional hazards and so a synthesis assuming constant hazards was considered appropriate
- In the second line network, proportional hazards were violated in one study in a comparator of interest, for nivolumab in the PD-L1≥1% subgroup for PFS only

The approach to conducting indirect comparisons for selpercatinib in the first and second line settings is described in Section B.2.8.1 and Section B.2.8.2, respectively.

B.2.8.1 First line treatment

LIBRETTO-001 single arm data for selpercatinib

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 compare selpercatinib to comparators of interest, it was therefore necessary to conduct an indirect treatment comparison; however, as LIBRETTO-001 was a single arm trial, there were no data available from a control arm that could be used to adjoin selpercatinib to an NMA. An NMA that included comparators of interest to the submission decision problem was also performed; the full methodology of this NMA is provided in Appendix D.1. The NMA included data from all randomised controlled trials (RCTs) identified in the first line to progression SLR, which met the feasibility inclusion criteria and reported OS, PFS or ORR. Due to the fact that selpercatinib was later adjoined to an existing NMA, data from treatments that are not relevant comparators included in the decision problem were included in the analysis.

Generation of pseudo-comparator arm and adjustment for *RET* and other prognostic factors

In order to connect the selpercatinib first line treatment arm of LIBRETTO-001 to the first line NMA, it was necessary to generate a pseudo-control arm. This pseudo-control arm was simulated for the LIBRETTO-001 trial using IPD available for the pemetrexed + platinum chemotherapy + 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.[67] 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 for those that may have a prognostic impact on trial endpoints (e.g.

smoking). This was not the case for *RET* fusion status because, although patients in KEYNOTE-189 were not tested for *RET* alterations, the prevalence of *RET* fusions is low in NSCLC (see Section B.1.3.1), and therefore it was likely that the proportion of patients with *RET* fusion-positive tumours was negligible in the trial. In contrast, all patients with NSCLC in the LIBRETTO-001 trial had *RET* fusion-positive tumours. Several studies have reported numerically superior outcomes for NSCLC patients with *RET* fusions (although the small number of patients included may inhibit these studies from reaching statistical significance)[68] and other studies have noted an association between *RET* fusion and known prognostic factors, such as having "never smoked".[69, 70]

In order to adjust the pseudo-control arm for the prognostic impact of having *RET* fusion-positive status, Eli Lilly and Company used data from the Flatiron Clinico-Genomic Database (CGDB). The CGDB is a longitudinal, demographically and geographically diverse database that contains electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care), including more than 2 million active US cancer patients. Available de-identified patient-level clinical data included structured data (e.g. laboratory values), unstructured data collected via technology-enabled chart abstraction from physician's notes (e.g. detailed biomarkers) and genomic data covering specimen features (e.g. mutation burden), alteration-level details (e.g. mutant allele count) and therapeutic recommendations that were reported to the clinician at the time of testing.

The patient cohort used to inform the adjustment of the pemetrexed + platinum arm included patients in the Flatiron CGDB who underwent comprehensive genomic profiling. Patients were selected from the CGDB who had advanced/metastatic NSCLC, were *RET*-fusion positive and who received systemic therapy. Adjustment was achieved using multivariable parametric survival models. These models were fitted to the Flatiron CGDB data, with multiple imputation of missing data, to obtain an estimate of the time acceleration factor for *RET* fusion-positive status, after taking account of other variables. Loglogistic models were selected based on model fit statistics presented in (Table 26). Point estimates for the time acceleration factors were used to adjust the survival times for PFS and OS for the KEYNOTE-189 pemetrexed + platinum chemotherapy + placebo trial arm; re-censoring to the original follow-up times for each patient was performed (Table 27).

Table 26. Multivariable parametric survival models fit results: Estimation of time acceleration factors for *RET* fusion-positive status in first line patients using Flatiron data

Survival model	PFS R^2	OS R^2
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File.

Table 27. Time acceleration factors for *RET* fusion-positive status in first line patients; estimated from Flatiron data

Survival model	PFS	OS
Time acceleration factor, mean (SE)	[redacted]	[redacted]

P value	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression free survival; SE: standard error.
Source: Eli Lilly and Company Ltd. Data on File.

Subsequently to adjusting the pseudo-control arm for *RET* fusion status, the IPD for pemetrexed + platinum + placebo were adjusted for further prognostic factors using a doubly robust technique, TMLE. TMLE was performed using the time-accelerated adjusted data to simultaneously model matched covariates from the pemetrexed + platinum + placebo and selpercatinib arms.

Nonparametric log-rank test and Cox regression models were performed on the resultant data from the process described above to obtain significance tests for the treatment effect and estimate log (HRs) and standard errors for selpercatinib versus the pseudo-control arm (Table 28). The HR was then introduced into the first line NMA.

Table 28. Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy in first line patients

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

Abbreviations: CI: confidence intervals; OS: overall survival; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File.

The Kaplan-Meier outputs for PFS and OS from the adjustment process outlined above are presented in Figure 18. The impact of the adjustment for *RET* fusion and other prognostic factors can be seen to have (artificially) improved PFS in both the KEYNOTE-189 pseudo-control arm and in the selpercatinib arm. It was not possible to adjust ORR data for *RET* fusion-positive status and other prognostic factors, as response data for the pemetrexed + platinum arm were not available in the Flatiron CGDB.

Figure 18. Kaplan-Meier charts for selpercatinib and pemetrexed plus platinum pseudo-control arm (original and adjusted for *RET* and other prognostic factors) in the first line (TMLE)

(A) PFS (B) OS

[redacted]

Abbreviations: OS: overall survival; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File.

First line network meta-analysis

A summary of the trials included in the first line NMA are presented in Appendix D.1.4, Table 15. The results of the first line NMA, providing comparative efficacy for selpercatinib and relevant comparators, are reported in the sections that follow.

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

The following subgroup analyses were also included in the first line analysis:

- Pembrolizumab in PD-L1–positive patients (≥50%)

Because there was no data available for PD-L1-positive patients treated with selpercatinib in the LIBRETTO-001 trial, the efficacy of selpercatinib in PD-L1-positive patients was assumed to be the same as in the overall *RET* fusion-positive population. There were also no subgroup data available for atezolizumab combination therapy; this comparator was therefore included in the main analysis.

Objective response rate

The network diagram for ORR in the first line setting for the whole population and PD-L1≥50% subgroup is shown in Figure 19.

Figure 19. Network diagram for treatments included in the NMA for ORR in the first line population

(A) Overall population

[redacted]

(B) PD-L1≥50% subgroup

[redacted]

Note 1: Thickness of edges is proportional to 1/SE.
Note 2: Numbers on each connection represents the number of trials informing that connection.
Note 3: The blue triangle represents a closed loop of evidence.
Abbreviations: ATEZc: atezolizumab; BEVc: bevacizumab; GEMi: gemcitabine; IPI: ipilimumab; NIVc: nivolumab; PACi: paclitaxel; PEMc: pemetrexed; PEMBROc: pembrolizumab; PLATi: platinum chemotherapy; SELc: selpercatinib.
Source: Eli Lilly and Company Ltd. Data on File.[71]

The relative treatment effect (OR) for ORR for comparators of interest in the first line population versus pemetrexed plus platinum chemotherapy are presented in Table 29, for both the overall population (A) and the PD-L1≥50% subgroup (B). Random effects model was chosen for the base case, except for the PD-L1≥50% subgroup, where a fixed effects model was used. An OR>1 is indicative of better response for the treatment in the row versus the reference treatment in the column. Forest plots are presented in Figure 20. Of all treatments included in the analysis, selpercatinib demonstrated the highest odds of inducing an ORR compared to pemetrexed plus platinum chemotherapy (OR: [redacted]; 95% CrI: [redacted]).

Table 29. Relative treatment effects expressed as pairwise ORs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for ORR in the first line treatment population

Treatment	Pairwise OR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]
Pembrolizumab (PD-L1≥50% subgroup)[a]	[redacted]

[a] The FE model was used for the subgroup analyses due to a convergence issue in the RE model.
Abbreviations: CrI: credible interval; NR: not reported; OR: odds ratio; ORR: objective response rate; PD-L1: programmed death-ligand 1.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Figure 20. Posterior median ORs of active treatments versus pemetrexed + platinum chemotherapy for ORR, first line treatment populations (random effects)

(A) Overall population

(B) PD-L1≥50% subgroup

[redacted]

Notes: (A) PEMBROc for the whole population is not a relevant intervention in UK clinical practice. A fixed effects model was used for the PD-L1≥50% subgroup
Abbreviations: ATEZc: atezolizumab; BEVc: bevacizumab; GEMi: gemcitabine; IPI: ipilimumab; NIVc: nivolumab; PACi: paclitaxel; PEMc: pemetrexed; PEMBROc: pembrolizumab; PLATi: platinum chemotherapy; SELc: selpercatinib.
Source: Eli Lilly and Company Ltd. Data on File.

Progression-free survival

The network diagrams for PFS in the first line setting for the whole population and the PD-L1≥50% subgroup is shown in Figure 21.

Figure 21. Network diagram for treatments included in the NMA for PFS in the first line population (random effects with informative priors)

(A) Overall population

[redacted]

(B) PD-L1≥50% subgroup

[redacted]

Note 1: Thickness of edges is proportional to 1/SE.
Note 2: Numbers on each connection represents the number of trials informing that connection.
Note 3: The blue triangle represents a closed loop of evidence.
Abbreviations: ATEZc: atezolizumab; BEVc: bevacizumab; GEMi: gemcitabine; IPI: ipilimumab; NIVc: nivolumab; PACi: paclitaxel; PEMc: pemetrexed; PEMBROc: pembrolizumab; PLATi: platinum chemotherapy; SELc: selpercatinib.
Source: Eli Lilly and Company Ltd. Data on File.

The relative treatment effects for interventions of interest for PFS in the first line population versus pemetrexed plus platinum chemotherapy are presented in Table 30, for both the overall population and the PD-L1≥50% subgroup. Random effects using informative priors was chosen for the base case. A lower HR is indicative of lower hazard of progression or death for the treatment in the row compared to the reference treatment in the column. Forest plots are presented in Figure 22. Of all treatments included in the analysis, selpercatinib demonstrated the lowest risk of disease progression compared to pemetrexed plus platinum chemotherapy (HR: [redacted]; [redacted]).

Table 30. Relative treatment effects expressed as HRs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for PFS in the first line treatment population (random effects with informative priors)

Treatment	Median HR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]
Pembrolizumab (PD-L1≥50% subgroup)	[redacted]

Abbreviations: CrI: credible interval; NR: not reported; HR: hazard ratio: PD-L1: programmed death-ligand 1.
Source: Eli Lilly and Company Ltd. Data on File.

Figure 22. Posterior median HRs of active treatments versus pemetrexed + platinum chemotherapy for PFS, first line treatment population (random effects with informative priors)

(A) Overall population

(B) PD-L1≥50% subgroup

[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio: PD-L1: programmed death-ligand 1; PEM + PLATi: pemetrexed + platinum chemotherapy; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.

Overall survival

The network diagrams for OS in the first line setting for the whole population and the PD-L1 L1≥50% subgroup is shown in Figure 23.

Figure 23. Network diagram for treatments included in the NMA for OS in the first line population (random effects)

(A) Overall population

[redacted]

(B) PD-L1≥50% subgroup

[redacted]

Note 1: Thickness of edges is proportional to 1/SE.
Note 2: Numbers on each connection represents the number of trials informing that connection
Note 3: The blue triangle represents a closed loop of evidence.
Abbreviations: ATEZc: atezolizumab; BEVc: bevacizumab; GEMi: gemcitabine; IPI: ipilimumab; NIVc: nivolumab; PACi: paclitaxel; PEMc: pemetrexed; PEMBROc: pembrolizumab; PLATi: platinum chemotherapy; SELc: selpercatinib.
Source: Eli Lilly and Company Ltd. Data on File.

The relative treatment effects for interventions of interest for OS in the first line population versus pemetrexed plus platinum chemotherapy are presented in Table 31, for both the overall population and the PD-L1≥50% subgroup. Random effects using informative priors was chosen for the base case. A forest plot for the PD-L1≥50% subgroup is presented in Figure 24. Mirroring PFS, selpercatinib demonstrated the lowest risk of death compared to pemetrexed plus platinum chemotherapy (HR: [redacted]; 95% CrI: [redacted]) compared with comparators included in the NMA.

Table 31. Relative treatment effects expressed as HRs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for OS in the first line treatment population (random effects with informative priors)

Treatment	Pairwise HR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]
Pembrolizumab (PD-L1≥50% subgroup)	[redacted]

Abbreviations: CrI: credible interval; NR: not reported; HR: hazard ratio: PD-L1: programmed death-ligand 1.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Figure 24. Posterior median HRs of active treatments versus pemetrexed + platinum chemotherapy for OS, first line treatment population (random effects with informative priors)

(A) Overall population

(B) PD-L1≥50% subgroup

[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival; PD-L1: programmed death-ligand 1; PEM + PLATi: pemetrexed + platinum chemotherapy.
Source: Eli Lilly and Company Ltd. Data on File.[71]

B.2.8.2 Second line treatment

Generation of pseudo-comparator arm to selpercatinib

The comparison of selpercatinib in second line advanced *RET* fusion-positive NSCLC against relevant comparators took a similar approach to the first line indirect treatment comparison (see Section B.2.8.1). The generation of comparative treatment effect estimates in the second line setting between selpercatinib and relevant comparators faced the same challenge in the form of only having single arm data available from the LIBRETTO-001 trial. Accordingly, as per the approach in the first line setting, a pseudo-comparator arm was generated through sourcing of IPD from the docetaxel + placebo arm of the REVEL RCT, which included patients with advanced, squamous or non-squamous NSCLC who had progressed after a first-line platinum-based chemotherapy regimen.[72] The same approach to that used in the first line treatment setting was adopted to adjust the pseudo-comparator docetaxel plus placebo arm for *RET* fusion-positive status, through application of a time-acceleration factor generated through analysis of the Flatiron CGDB. Loglogistic models were selected based on model fit statistics to estimate the time-acceleration factor (Table 36).

Table 32. Multivariable parametric survival models fit results: Estimation of time acceleration factors for *RET* fusion-positive status in second line patients using Flatiron data

Survival model	PFS R^2	OS R^2
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Table 33. Time acceleration factors for *RET* fusion-positive status in second line patients; estimated from Flatiron data

Survival model	PFS	OS
Time acceleration factor, mean (SE)	[redacted]	[redacted]
P value	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression free survival; SE: standard error.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Subsequent performance of TMLE as per the first line setting generated a treatment effect between selpercatinib and docetaxel plus placebo (Table 34). The detailed methodology for this approach is described in Appendix D.1.7 (for both first and second line treatment settings).

Table 34. Estimated treatment effects for selpercatinib versus docetaxel in second line patients

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

Abbreviations: CI: confidence intervals; OS: overall survival; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on File.[71]

The Kaplan-Meier outputs for PFS and OS from the adjustment process outlined above are presented in Figure 25. The impact of the adjustment for *RET* fusion and other prognostic factors can be seen to have (artificially) improved both PFS and OS in REVEL, whilst the adjustment had little effect on selpercatinib.

Figure 25. Kaplan-Meier charts for selpercatinib and docetaxel plus placebo pseudo-comparator arm (original and adjusted for *RET* and other prognostic factors) in the second line (TMLE)

(A) PFS

(B) OS

[redacted]

Source: Eli Lilly and Company Ltd. Data on File.[71]

Second line network meta-analysis

An NMA was similarly performed including all comparators of interest at the second line, as described in Appendix D.4. A summary of included studies is provided in Appendix D.4.5, Table 33. The NMA included data from all RCTs identified in the second line SLR, which met the feasibility assessment inclusion criteria and reported OS, PFS or ORR. Due to the fact that selpercatinib was later adjoined to an existing NMA, data from treatments that are not relevant comparators in the decision problem were included in the analysis.

The results of the second line NMA, providing comparative efficacy for selpercatinib and relevant comparators, are reported in the sections that follow. To note, only pooled dose data (2 mg/kg and 10 mg/kg) for the pembrolizumab PD-L1 subgroup were available from KEYNOTE-010. This data is therefore used in the NMA.

For ORR, the proportion of patients who experienced an objective response was modelled and treatment effects were presented as ORs with associated 95% CrIs. OS and PFS HRs, representing treatment effects with corresponding standard error values, were synthesised in the model. A hierarchical exchange model was used to take account the PD-L1 as a class in the model, therefore subgroups analyses were not performed for nivolumab and pembrolizumab in PD-L1≥50% patients. Age was significant and included in the model; the results were centred on 61 years of age (the mean age of the second line NSCLC population in LIBRETTO-001).

Objective response rate

The network diagram for ORR in the second line setting is shown in Figure 26.

Figure 26: Network diagram for treatments included in the NMA for ORR in the second line population

[redacted]

Abbreviations: NMA: Network meta-analyses; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[71]

The relative treatment effects for interventions of interest for ORR in the second line population versus docetaxel are presented in Table 35, for both the overall population and the PD-L1≥1% subgroup. Forest plots are presented in Figure 27. ORR data were not available for atezolizumab or pembrolizumab and therefore it was not possible to generate a relative treatment effect for these therapies versus docetaxel.

Of all the treatments included in the analysis, selpercatinib demonstrated the highest odds of inducing an ORR compared to docetaxel plus placebo (OR: [redacted]; 95% CrI: [redacted].

Table 35. Relative treatment effects expressed as ORs versus docetaxel (with 95% CrI) for ORR in the second line treatment population (fixed effects)

Treatment	Median OR (95% CrI) versus docetaxel + placebo
Selpercatinib	[redacted]
Nivolumab (PD-L1≥1%)	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; ORR: objective response rate; PD-L1: programmed death-ligand 1.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Figure 27: Forest plot of relative treatment effects for selpercatinib and comparator interventions versus docetaxel for ORR in the second line treatment population (fixed effects)

[redacted]

Abbreviations: CI: Credible interval; HR: hazard ratio; NA: not applicable; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Progression-free survival

The network diagram for PFS in the second line setting is shown in

Figure 28.

Figure 28. Network diagram for treatments included in the NMA for PFS in the second line population

[redacted]

Note: Numbers on each connection represents the number of trials informing that connection
Source: Eli Lilly and Company Ltd. Data on File.[71]

The relative treatment effects for interventions of interest for PFS in the second line population versus docetaxel are presented in Table 36, for both the overall population and the PD-L1≥1% subgroup. Forest plots are presented in Figure 29. PFS data were not available for atezolizumab and therefore it was not possible to generate a relative treatment effect for atezolizumab versus docetaxel.

Of all the treatments included in the analysis, selpercatinib demonstrated the lowest risk of disease progression compared to docetaxel plus placebo (HR: [redacted] 95% CrI: [redacted].

Table 36. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for PFS in the second line treatment population (fixed effects hierarchical exchange)

Treatment	Median HR (95% CrI) versus docetaxel + placebo
Selpercatinib	[redacted]
Nivolumab (PD-L1≥1%)	[redacted]
Pembrolizumab (PD-L1≥1%)	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio: PD-L1: programmed death-ligand 1; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Figure 29. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel for PFS in the second line treatment population (fixed effects hierarchical exchange)

[redacted]

Abbreviations: CI: credible interval; DOC: docetaxel; HR: hazard ratio; NA: not applicable; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Overall survival

The network diagrams for OS in the second line setting is presented in

Figure 30.

Figure 30. Network diagram for treatments included in the NMA for OS in the second line population

[redacted]

Note: Numbers on each connection represents the number of trials informing that connection.
Source: Eli Lilly and Company Ltd. Data on File.[71]

The relative treatment effects for interventions of interest for OS in the second line population versus docetaxel plus placebo are presented in Table 37, for both the overall population and the PD-L1≥1% subgroup. Forest plots are presented in Figure 31. Selpercatinib demonstrated the lowest risk of death compared to docetaxel plus placebo of all treatments included in the analysis (HR: [redacted]; 95% CrI: [redacted].

Table 37. Relative treatment effects expressed as HRs versus docetaxel plus placebo (with 95% CrI) for OS in the second line treatment population (fixed effects hierarchical exchange)

Treatment	Median HR (95% CrI) versus docetaxel + placebo
Selpercatinib	[redacted]
Atezolizumab	[redacted]
Nivolumab (PD-L1≥1%)	[redacted]
Pembrolizumab (PD-L1≥1%)	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio; OS: overall survival; PD-L1: programmed death-ligand 1.
Source: Eli Lilly and Company Ltd. Data on File.[71]

Figure 31. Forest plot of relative treatment effects for selpercatinib and relevant comparator interventions versus docetaxel for OS in the second line treatment population (fixed effects hierarchical exchange)

[redacted]

Abbreviations: CI: credible interval; DOC: docetaxel; HR: hazard ratio; NA: not applicable; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File.[71]

B.2.8.3 Uncertainties in the indirect treatment comparisons

As discussed in Section B.2.8.1, 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 both the first line and second line NMA, a process which is associated with inherent uncertainty. However, a rich data source in the form of the Flatiron CGDB was leveraged in order to understand the impact of *RET* fusion-positive status on survival outcomes. Whilst the CGDB is US-based, the large number of NSCLC patients included in the database is anticipated to provide highly informative insights into the prognostic impact of genetic markers and other patient characteristics. Indeed, real-world evidence collected by Flatiron are already being utilised to compare survival estimates from clinical trials to survival data in patient records in order to evaluate opportunities to reduce uncertainty in the estimation of long-term outcomes.[73] In addition to *RET* fusion status, further differences in prognostic factors between LIBRETTO-001 and the pemetrexed plus platinum arm from KEYNOTE-189, as well as the docetaxel plus placebo arm from REVEL, were adjusted for, using the doubly robust TMLE method. A minor limitation is that whilst the pseudo-comparator arms in the first line and second line setting were adjusted for *RET* fusion status and other prognostic factors it was not possible to adjust the remainder of the network in the same way, instead HRs estimated from the NMAs were applied to the pseudo-control arms to estimate the treatment effect for relevant comparators for the submission. Also, further TMLE-adjustment for additional prognostic factors may have overestimated the treatment effect for pseudo-control arms to connect the first and second line NMAs compared to adjusting for RET-fusion alone by applying the time-acceleration factor. This was evident for the second line pseudo-control arm where the relative difference reduced substantially compared to the same adjusted selpercatinib arms, and to adjustments made to the first line control and selpercatinib arms.

As discussed in Appendix D.1.6, assessment of proportional hazards in the first line setting identified that in seven studies informing the PFS network and three studies informing the OS network, there was evidence that the proportional hazards assumption may not have held. In the second line network, proportional hazards were violated in one study (for a comparator of interest) for nivolumab in the PD-L1≥1% subgroup for PFS only. Nevertheless, for the majority of relevant comparators, there was no clear violation of proportional hazards for both first and second line, and it was therefore deemed appropriate to synthesise HRs, assuming constant hazards.

B.2.9 *Adverse reactions*

Summary of LIBRETTO-001 safety analysis

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (regardless of tumour type or treatment history) and specifically in those patients with *RET* fusion-positive NSCLC
    - [redacted] of patients in the OSAS and [redacted] of patients in the NSCLC SAS received the proposed starting dose of 160 mg BID. Dose reductions were required in [redacted] of the OSAS and [redacted] of the *RET* fusion-positive NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted] in the OSAS and NSCLC SAS, respectively)

- In the OSAS and the *RET* fusion-positive NSCLC SAS, permanent discontinuation of selpercatinib due to TEAEs were infrequent [redacted], with no predominant pattern among the individual AEs reported
- In the OSAS, Grade 3 or 4 TEAEs were reported in [redacted] patients and [redacted] in the *RET* fusion-positive NSCLC SAS, irrespective of relatedness to selpercatinib. 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 = [redacted]) 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 16th December 2019 data cut-off date
- The *RET* fusion-positive NSCLC Safety Analysis Set (SAS) (N = 329) 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 16th December 2019 data cut-off date

All AEs, from the time the informed consent form was signed until the end of the safety follow-up period (28 ± 7 days post last dose), were recorded on the appropriate electronic case report form (eCRF).[45] 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.[45]

B.2.9.1 Treatment duration and dosage

Informed by the Phase I dose escalation stage of LIBRETTO-001, the R2PD was 160 mg BID. The range of starting doses and average time on treatment for NSCLC patients in the study are summarised in Table 38. [redacted] ([redacted]/[redacted]) of patients in the OSAS received the proposed starting dose of 160 mg BID, for [redacted] ([redacted]) patients as a starting dose and for [redacted] ([redacted]) patients as a protocol-specified dose adjustment.[45] In the NSCLC SAS, most patients ([redacted]) received a starting dose of 160 mg BID and the mean time on treatment was [redacted] months with a range between [redacted] and [redacted] months. The mean relative dose intensity was [redacted] in the NSCLC SAS (Table 39).

Dose reductions were required in [redacted] of the OSAS and [redacted] of the *RET* fusion-positive NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted], respectively) (Table 40).[45] 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.[45]

Table 38. Selpercatinib dosing (Safety Analysis Sets)

	RET fusion-positive NSCLC (N = 329)	Overall population (N = [redacted])
Starting dose, n (%)		
20 mg QD	[redacted]	[redacted]
20 mg BID	[redacted]	[redacted]
40 mg BID	[redacted]	[redacted]
60 mg BID	[redacted]	[redacted]
160 mg QD	[redacted]	[redacted]
80 mg BID	[redacted]	[redacted]
120 mg BID	[redacted]	[redacted]
160 mg BID (RP2D)	[redacted]	[redacted]
200 mg BID	[redacted]	[redacted]
240 mg BID	[redacted]	[redacted]
Time on treatment, months		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[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 (16th December 2019 cut-off).[45]

Table 39. Selpercatinib relative dose intensity (Safety Analysis Sets)

	RET fusion-positive NSCLC (N = 329)	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]

Abbreviations: NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

Table 40. Selpercatinib dose modifications (Safety Analysis Sets)

	RET fusion-positive NSCLC (N = 329)	Overall population (N = [redacted])
Dose reduction, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	[redacted]
Intra-patient dose escalation	[redacted]	[redacted]
For other reason	[redacted]	[redacted]
Dose interruption, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	[redacted]
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]

Footnotes: [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 (16th December 2019 cut-off).[45]

B.2.9.2 Summary of adverse events

Adverse events were graded by the Investigator, when applicable, using the National Cancer Institute Common Terminology Criteria for Adverse Events.[74] In the event of an AE for which no grading scale existed, the Investigator classified the AE using the following criteria:

- Mild (Grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- Moderate (Grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- Severe (Grade 3) – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity
- Life-threatening (Grade 4) – An event that puts the patient at immediate or potential risk of death
- Fatal (Grade 5)

In the OSAS, [redacted] of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with [redacted] classed as Grade 3 or Grade 4 (Table 41).[45] A similar pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent [redacted] in the OSAS, with no predominant pattern among the individual AEs reported. No deaths within 28 days of last dose were attributed to selpercatinib. All were attributed to either disease progression ([redacted]), to an AE unrelated to the drug or to unknown reasons.[45]

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 41. Summary of safety trends (Safety Analysis Sets)

	RET fusion-positive NSCLC (N = 329)	Overall population (N = [redacted])
Any AE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Grade 3 or 4 AE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
AE leading to treatment discontinuation, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
SAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Fatal AE (none related to selpercatinib)	[redacted]	[redacted]

Abbreviations: AE: adverse event; NSCLC: non-small cell lung cancer; *RET* rearranged during transfection; SAE: serious adverse event.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

B.2.9.3 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.

A high proportion of patients in the OSAS ([redacted]) experienced at least 1 TEAE during treatment. The most common TEAEs in the OSAS were: dry mouth ([redacted]), diarrhoea ([redacted]), hypertension ([redacted]), aspartate aminotransferase (AST) increase ([redacted]), alanine transaminase (ALT) increase ([redacted]), fatigue ([redacted]), constipation ([redacted]), peripheral oedema ([redacted]), headache ([redacted]) and nausea ([redacted]).[45] 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 42.[45]

Table 42. Common treatment-emergent adverse events of all grades (15% or greater in any Safety Analysis Sets)

Preferred term	Maximum severity incidence, n (%)	
	RET fusion-positive NSCLC (N = 329)	Overall population (N = [redacted])

	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombo-cytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[45]

B.2.9.4 Grade 3–4 adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in [redacted] patients, irrespective of relatedness to study drug (Table 43). The most common Grade 3–4 events were hypertension ([redacted]), ALT increase ([redacted]), AST increase ([redacted]) and hyponatraemia ([redacted]). Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion ([redacted] were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, [redacted] patients experienced Grade 3–4 TEAS, irrespective of relatedness to selpercatinib (Table 43). A smaller proportion ([redacted] [[redacted]) were considered by the Investigator to be related to selpercatinib. Common TEAES mirrored the OSAS analysis set.[45]

Table 43. Grade 3–4 adverse events in 2% or more of patients (Safety Analysis Sets)

Preferred term	*RET* fusion-positive NSCLC (N = 329)	Related to selpercatinib (*RET* fusion-positive NSCLC) (N = 329)	Overall population (N = [redacted])	Related to selpercatinib (overall population) (N = [redacted])
1 or more Grade 3–4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropoenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]

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 (16th December 2019 cut-off).[45]

B.2.9.5 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.[45]

ALT/AST increase

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 related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[45] 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.[45]

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.[45]

In the OSAS, drug hypersensitivity was observed in a [redacted] of patients who had one or more AE of hypersensitivity. [redacted] patients had a single event; [redacted] had multiple events (range [redacted]). The median time to first onset was [redacted] weeks (range: [redacted]). Eleven patients ([redacted]) experienced Grade 3 as the worst severity and there were no Grade 4 hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted] OSAS patients.[45]

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, dose interruption or both. Only 3 of the [redacted] patients were reported to permanently discontinue selpercatinib due to a hypersensitivity reaction.[45]

Hypertension

In the OSAS, the AE of hypertension was reported in [redacted] of patients ([redacted] considered related to selpercatinib), with [redacted] of patients having experienced Grade 3–4 AEs of hypertension ([redacted] Grade 3–4 and related to selpercatinib). A similar proportion of NSCLC SAS patients experienced hypertension ([redacted]), with [redacted]) classified as Grade 3–4.[45]

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. A minority of OSAS patients required dose interruption ([redacted] considered related to selpercatinib) and/or reduction ([redacted] considered related to selpercatinib). No patients discontinued therapy due to an AE of hypertension.[45]

Notable Event-QT Prolongation

Any grade ECG QT prolongation was reported for [redacted] patients ([redacted]), with [redacted] considered related to selpercatinib in the OSAS. The majority of events were Grade 1 or Grade 2. One 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.[45]

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.[45]

B.2.9.6 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. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent [redacted], 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*.

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 appraisal, based on an additional data cut.

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.[2] Results for LIBRETTO-431 are expected in December 2023.[2] It is not anticipated for any data from this trial to become available during the course of this appraisal. Should selpercatinib receive a recommendation for use on the CDF, data would be collected from LIBRETTO-431 during the course of CDF funding.

B.2.11 *Innovation*

As discussed in Section B1, there are currently no targeted therapeutic options available on the NHS for *RET* fusion-positive NSCLC patients in either the first or second line setting; the current conventional pharmacological therapy options recommended by NICE, and used routinely on the NHS for these patients, include immunotherapies and non-targeted chemotherapy.[10] However, selpercatinib has demonstrated clinical benefit by directly targeting *RET* as an underlying driver of disease amongst patients with *RET* fusion-positive NSCLC. The magnitude, durability and speed of the response rate observed in the LIBRETTO-001 trial represents a therapeutic innovation, with the potential to prolong patient quality of life.[45]

Treatment with systemic and non-targeted therapies currently available on the NHS can result in debilitating side effects for patients, which further reduces their HRQoL in addition to the burden caused by the disease itself.[54, 55] Combined with this, a real-world study of patient outcomes in the UK has shown that a large number (45%) of NSCLC patients treated with first line chemotherapy subsequently received second line therapy, suggesting that there is an unmet need for more efficacious first line options in advanced non-squamous NSCLC.[54] With regards to immunotherapy, although the availability of commonly used treatments in the UK, such as pembrolizumab and nivolumab, have provided additional treatment options, response rates reported in clinical trials involving advanced non-squamous NSCLC patients in both the first and second line setting are below 50% (KEYNOTE-189 [first line]: pembrolizumab + chemotherapy

ORR = 47.6%; CheckMate057 [second line]: nivolumab ORR = 19%).[75, 76] In addition, common immunotherapies are administered intravenously,[75, 76] which adds additional costs to the NHS in terms of administration at hospitals,[77] and adverse events from immunotherapies can affect one or several different systemic organ systems, with an incidence of Grade 3 and higher toxicities during NSCLC treatment of 7–13%, according to the Society for Immunotherapy of Cancer.[55]

Selpercatinib is a first-in-class oral treatment, providing advantages in terms of ease of administration and patient preference compared with intravenous medication,[78] that has demonstrated a high specificity for *RET* and consequently a favourable efficacy profile in first line *RET* fusion-positive NSCLC patients, with a very high ORR of 85%.[45] Selpercatinib has also demonstrated favourable efficacy results in patients at the second line or greater, with an ORR of [redacted] in previously treated patients.[45] When compared against pemetrexed plus platinum chemotherapy (first line) and docetaxel (second line) through ITC, selpercatinib demonstrated the highest odds of inducting a tumour response of all treatments included in the analysis, in both the first line (OR: [redacted]; 95% CrI: [redacted]) and second line (OR: [redacted]; 95% CrI: [redacted] treatment setting.

In addition to the magnitude of ORR observed, the DOR in patients with *RET* fusion-positive NSCLC observed in LIBRETTO-001 contributes to demonstrating patient benefit in terms of maintaining their quality of life for a longer period of time. Although PFS and OS data are immature, early results suggest that selpercatinib provides a high level of disease control (estimated proportion of first line patients progression free at 12 months: [redacted]; second line [PAS]: [redacted]), and consequently is likely to contribute to improvements in OS (estimated proportion of first line patients alive at 12 months: [redacted]; second line [PAS]: [redacted]). When compared against pemetrexed plus platinum chemotherapy (first line) and docetaxel (second line) through ITC, selpercatinib demonstrated the lowest risk of disease progression (first line HR: [redacted]; second line HR: [redacted]) and death (first line HR: [redacted]; second line HR: [redacted]) in both the first line and second line treatment settings.

In line with its specificity to *RET*, selpercatinib is also well-tolerated and clinically manageable, with Grade 3 or 4 TEAEs reported at [redacted], dose reductions seen in [redacted], and a study drug discontinuation rate due to AEs related to selpercatinib of [redacted] in patients with advanced NSCLC.[45] In contrast, a trial of pembrolizumab + chemotherapy, a comparator to selpercatinib in the first line setting, reported a Grade 3 or higher AE occurrence of 67.2% and a noticeably higher drug discontinuation rate (13.8%).[75] Because toxicities related to selpercatinib are reversable through dose interruption or addressable through dose reduction or use of concomitant medication, discontinuation was low in LIBRETTO-001, meaning patients could experience consistent benefit from the highly efficacious anti-tumour activity of selpercatinib. A potent and highly selective *RET* inhibitor, like selpercatinib, therefore offers advantages in the treatment of *RET* fusion-positive NSCLC patients, irrespective of line of treatment.

Crucially, targeted therapy is now considered the preferred initial treatment for patients with actionable mutations and consequently molecular profiling of NSCLC tumours is recommended by international consensus guidelines as part of routine evaluation in newly diagnosed patients.[79] Introduction of selpercatinib into routine clinical practice in England will encourage accelerated establishment of the NHS genetic hubs and increased, as well as more rapid, tumour testing for genetic abnormalities, enabling patients to access personalised treatment for their cancer.[18]

Overall, with clinically meaningful ORRs across lines of therapy and a well-tolerated, clinically manageable, safety profile, selpercatinib demonstrates a favourable benefit-risk profile for use by the NHS in patients with *RET* fusion-positive NSCLC who require systemic therapy and another important step towards the establishment of targeted treatment as standard of care for non-squamous NSCLC.

B.2.12 *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 adults with advanced non-squamous *RET* fusion-positive NSCLC, in both the first line (treatment naïve) and second line (pre-treated) setting. 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.[45]

A high ORR was observed in advanced *RET* fusion-positive NSCLC patients during both first line (85%) and second line (IAS: [redacted]) selpercatinib treatment. These results provide tangible evidence for the anti-tumour activity of selpercatinib in advanced NSCLC, irrespective of the line of treatment. In addition, with [redacted] of first line and [redacted] of second line (IAS) 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. Although PFS and 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.[80, 81] Kaplan-Meier estimates suggest that [redacted] of first line and [redacted] of second line (IAS) patients will remain progression free at 12 months, indicating a high level of disease control and stabilisation with selpercatinib, which is supported by a high predicted OS across treatment settings (first line: [redacted]; second line [IAS]: [redacted]). Crucially, these clinical outcomes are supported by patient reported outcomes, with [redacted] of evaluated patients reporting an improvement in their global health status via EORTC-QLQ-C30 during Cycle 9 of treatment.

The results of the ITC indicated that selpercatinib was associated with a statistically significant improvement in ORR compared with pemetrexed plus platinum chemotherapy in the first line treatment setting (OR: [redacted]) and second line treatment setting (OR: [redacted]) (Section B.2.8.1). Similarly, results from the ITC indicated that selpercatinib was associated with a statistically significant lower risk of disease progression and a lower risk of death when compared with pemetrexed plus platinum chemotherapy in the first line (PFS HR: [redacted]; OS HR: [redacted]), using IPD from KEYNOTE-189,[67] and docetaxel in the second line (PFS HR: [redacted]; OS HR: [redacted]), using IPD from REVEL (Section B.2.8.2).[72]

Selpercatinib has also demonstrated a tolerable safety profile across all trial patients (regardless of tumour type), with Grade 3–4 AEs seen in [redacted] of patients in the OSAS, a [redacted] dose reduction rate and a discontinuation rate due to AEs of [redacted]. Similar results were reported in patients with *RET* fusion-positive NSCLC specifically, with Grade 3–4 AEs reported in [redacted] patients, dose reductions reported in [redacted] of patients and discontinuations in [redacted] (related to selpercatinib) of patients. 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 patients with advanced (Stage III 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 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 included both first line and second line patients with confirmed advanced, non-squamous, *RET* fusion-positive NSCLC, which is the patient population under consideration in this submission. Although [redacted] and [redacted] of the PAS and IAS populations received prior MKI treatment respectively, which is not approved for use on the NHS, clinical experts affirmed that the patient population of the LIBRETTO-001 trial was otherwise generalisable to clinical practice in the UK.[10] The molecular sequencing of tumour samples was also consistent with NHS practice, once the transition to Genomic Hubs has been completed, with [redacted] of PAS patients assessed using NGS.[18]

[redacted] based in the UK, enrolling [redacted] patients into the OSAS and [redacted] into the overall NSCLC population. However, the high proportion of patients identified as Asian (first line: [redacted]; second line: [redacted]), the higher proportion of women (first line: [redacted]; second line: [redacted]), the low median age at diagnosis for NSCLC (first line: [redacted] and second line: [redacted]) and the higher proportion of patients that have never smoked (first line: [redacted]; second line: [redacted]) compared to the general lung cancer population, is consistent with the patient profile for *RET* fusion-positive NSCLC reported in the literature,[4, 13] and is anticipated to mirror the real-world patient profile in England. 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.[14] 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 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 *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 first and second line NMAs introduced inherent uncertainty. However, both pseudo-comparator arms from the KEYNOTE-189 and REVEL trials were adjusted for *RET*-status and other prognostic factors using Flatiron data and the doubly robust TMLE method. Further TMLE-adjustment for additional prognostic factors may have overestimated the treatment effect for the pseudo-control arms to connect the first and second line NMAs compared to adjusting for RET-fusion alone by applying the time-acceleration factor. This was more evident for the second line pseudo-control arm where the relative difference reduced dramatically compared to the same adjusted selpercatinib arms. Clinical expert opinion challenged the estimation by TMLE for the pseudo-control arms compared to the selpercatinib and confirmed this was likely an overestimation. Therefore, the relative difference between the pseudo-control, and thus comparators, is likely to be underestimated and conservative.

In addition, for seven first line studies informing the PFS network and three studies informing the OS, the assumption of proportional hazards did not hold. In the second line, the assumption of proportional hazards did not hold for one study informing the PFS network. However, as most studies did not violate proportional hazards, a synthesis assuming constant hazards was considered appropriate.

PFS and OS data from LIBRETTO-001 were also immature, with only [redacted] of first line patients (SAS1) having experienced disease progression and [redacted] having died at the latest data cut-off date. PFS and OS data were also immature for the second line (PAS) setting ([redacted] of patients experienced disease progression and [redacted] died at the latest data cut-off), although median PFS was reached ([redacted] months). Although initial results from LIBRETTO-001 are promising, confirmatory data supporting the effect of selpercatinib on PFS and OS is therefore desirable.

To confirm the benefits of selpercatinib in *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 patients who have not received prior therapy for metastatic *RET* fusion-positive NSCLC, which is planned to enrol ~250 participants. The primary endpoint is PFS by IRC and the study includes a comparator arm of pembrolizumab combination therapy. It is therefore planned for preliminary clinical effectiveness and safety data for selpercatinib versus a comparator relevant to the decision problem 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 may be data available from an additional cut-off during the NICE appraisal process for selpercatinib, which may provide PFS and OS data with increased maturity. Should selpercatinib be recommended under the CDF, it is anticipated that mature OS and PFS would be available prior to evaluation for exit of the CDF.

Selpercatinib as an end-of-life therapy

Evidence to support the consideration of selpercatinib as an end-of-life treatment in the context of NICE's end-of-life criteria are summarised in Table 44. Patients with advanced (Stage IIIb or IV), *RET* fusion-positive, non-squamous NSCLC who are treated at the second line setting with nintedanib plus docetaxel are anticipated to have a short duration of survival, at less than 24 months.[82] The results of the base case cost-effectiveness analysis, presented in Section B.3.7, support this, and also demonstrate that selpercatinib is associated with a substantially longer OS estimate than nintedanib and docetaxel, at [redacted] months versus [redacted] months, respectively. As such, selpercatinib met end-of-life criteria in the second line treatment setting in the comparison with nintendanib plus docetaxel.

Table 44. End-of-life criteria

Criterion	Data available

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Yes –** The results of the base case cost-effectiveness analysis (Section **Error! Reference source not found.**) demonstrated that nintedanib plus docetaxel had a predicted survival of [redacted] months, however, as described in Section B.3.3.2, feedback from the clinical expert was that the adjustment made to the nintedanib + docetaxel comparator, through application of the time acceleration factor to adjust for *RET* fusion-positive status and TMLE, had resulted in overly optimistic OS estimations for comparators. The median OS of [redacted] months is therefore considered an overestimation of survival for nintedanib + docetaxel. This is further supported by a median OS of 12.6 months reported in the LUME-Lung 1 trial[82]
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally at least an additional 3 months, compared with current NHS treatment	**Yes** – As described above, the median OS for nintedanib + docetaxel was [redacted] months, whilst the median OS for selpercatinib was [redacted] months. This [redacted] emphasises the survival benefit of selpercatinib compared with current NHS treatment and meets the 3-month additional survival target.

Abbreviations: NHS: National Health Service; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection; TMLE: targeted minimum loss-based estimation.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis for selpercatinib in NSCLC

- A *de novo* cost-effectiveness model was developed to assess the cost effectiveness of selpercatinib in adults with *RET* fusion-positive NSCLC
- Two key populations were considered in the economic analysis:
  - Adults undergoing **first line treatment** for non-squamous *RET* fusion-positive NSCLC, informed by data from the SAS1 population (N=39) from the LIBRETTO-001 trial
  - Adults undergoing **second line treatment** for non-squamous *RET* fusion-positive NSCLC, informed by data from the IAS (N=185) population from the LIBRETTO-001 trial
- In the **first line setting analysis**, the cost-effectiveness of selpercatinib in the following patient groups was assessed:
  - All patients: selpercatinib versus pembrolizumab combination
  - PD-L1 TPS≥50%: selpercatinib versus pembrolizumab
  - PD-L1 TPS<50%: selpercatinib versus atezolizumab combination therapy
- In the **second line setting analysis**, the cost-effectiveness of selpercatinib in the following patient groups:
  - All patients: selpercatinib versus nintedanib + docetaxel and atezolizumab
  - PD-L1 TPS≥1%: selpercatinib versus nivolumab and pembrolizumab
- 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 survival data for selpercatinib and the pseudo-control (reference) arms generated through the process described in Section B.2.8
  - In the first line setting, survival analysis was conducted for PFS and PPS (assuming this was equivalent for all interventions), whilst in the second line setting, it was conducted for PFS and OS
- In order to generate extrapolations for comparators to selpercatinib in the first and second line settings for PFS and OS, the HRs generated through the NMAs were applied to the reference arms
- Expert clinical opinion was sought to determine the most clinically plausible extrapolations for selpercatinib, the reference arms and comparators
- In the first line setting, for PFS, the stratified lognormal and unstratified Gompertz curves were selected for selpercatinib and the reference (and comparator) arms, respectively. In the second line setting, for PFS, the stratified gamma and unstratified Weibull curves were selected for selpercatinib and the reference (and comparator) arms, respectively. For OS, the unstratified Gompertz and unstratified Weibull were selected for selpercatinib and the reference (and comparator) arms, respectively.
- Costs included in the model were for drug acquisition, administration, monitoring, subsequent therapies, health state costs, adverse events and end of life costs
- Utility values were derived from TA621[83] for the first line population and TA484[84] in the second line population

Base case cost-effectiveness results

- The results illustrate that in all patient groups across both treatment lines versus all comparators, selpercatinib is associated with greater QALYs and LYG, reflecting the high levels of efficacy of selpercatinib in the first line *RET* fusion-positive NSCLC population
- For the **first line** population selpercatinib was associated with pairwise ICERs of [redacted], [redacted] and [redacted] per QALY gained, for pembrolizumab combination, atezolizumab combination and pembrolizumab monotherapy (PDL1≥50% subgroup), respectively.
- For the second line population, selpercatinib was associated with pairwise ICERs of [redacted], [redacted], [redacted] and [redacted] per QALY gained versus nintedanib + docetaxel, atezolizumab, nivolumab (PDL1≥1% subgroup) and pembrolizumab (PDL1≥1% subgroup), respectively.
- It should be noted that for both populations these results are presented at list price for selpercatinib and comparators, [redacted].

Sensitivity and scenario analyses

- The results of the probabilistic base case were closely reflective of the deterministic analysis, demonstrating that the model is robust to variation in input parameters. This was mirrored in the results of the deterministic sensitivity analyses, where only a small number inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons and both treatment lines
- 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 PFS. As noted above, significant importance was placed on the clinical plausibility of the extrapolations used in the base case, with feedback sought from an expert oncologist practicing in the NHS in order to ensure the selection of the most appropriate functions.

Conclusions

- The results of the cost-effectiveness analysis demonstrate that compared to all comparators across both the first and setting line settings, selpercatinib is associated with an extension to life and an improvement in HRQoL, as illustrated by the accrual of a greater number of QALYs and LYG across all comparisons.
- Selpercatinib was not found to represent a cost-effective use of NHS resources when considered at list price, with ICERs above the £30,000 per QALY threshold versus relevant comparators in both populations and above £50,000 per QALY threshold where end-of-life criteria are applicable.
- [redacted]

B.3.1 *Published cost-effectiveness studies*

Selpercatinib is a first in class therapy for adults with *RET* fusion-positive NSCLC. As such, there have been no previous cost-effectiveness studies published for a selective RET kinase inhibitor in this population specifically. However, cost-effectiveness models have been developed previously for interventions for the treatment of advanced and metastatic NSCLC, including where alternative genetic markers to RET are expressed. The approaches to identifying relevant cost-effectiveness studies in the first line and second line setting are described below.

First line treatment

In order to identify previous cost-effectiveness studies relevant to modelling the first line *RET* fusion-positive NSCLC population, economic evaluations were identified from a previous SLR designed to identify cost-effectiveness studies in advanced and/or metastatic EGFR-positive NSCLC, for which searches were conducted on 4th March 2019. Search strategies were used which did not specify any oncogenic driver, therefore, the 48 articles excluded from this SLR during the full-text review as they were not specifically EGFR focussed were used as the basis of the search for cost-effectiveness studies in first line patients for this submission. In addition, a targeted search was performed to identify published information from key HTA bodies in order to inform the cost-effectiveness model for selpercatinib. Full details of the SLR methodology and results can be found in Appendix G.

Second line treatment

An SLR was conducted to identify the utility, resource use and cost data needed to inform economic modelling for selpercatinib in advanced NSCLC treated at second line, with searches taking place on 12th August 2019. Economic analyses and systematic reviews that were identified in this search were included at the first stage of screening, used for identification of primary studies, and then excluded at a later level of screening. Economic evaluations were not explored further due to the large number of studies captured in the first line SLR, and the number of prior cost-effectiveness models in NSCLC submitted to NICE that could inform the model for selpercatinib. Full details of the SLR methodology can be found in Appendices H and I.

B.3.2 *Economic analysis*

As described in Section B.3.1, no prior economic analyses for *RET* fusion-positive advanced NSCLC have been conducted. Accordingly, a *de novo* cost-effectiveness model was developed to assess the cost effectiveness of selpercatinib in adults with *RET* fusion-positive NSCLC in patients receiving treatment in the first or second line setting.

Sections B.3.2.1, B.3.2.2 and 0 present the patient populations, the model structure and the included interventions and comparators, respectively.

B.3.2.1 Patient population

Two populations are considered in the economic analysis:

- Adults undergoing **first line treatment** for non-squamous *RET* fusion-positive NSCLC, informed by data from the SAS1 population (N=39) from the LIBRETTO-001 trial
    - The SAS1 population of LIBRETTO-001 comprised *RET* fusion-positive NSCLC patients treated with selpercatinib as of the cut-off date who had received no prior systemic therapy (see Section B.2.3.3 for further details)
- Adults undergoing **second line treatment** for non-squamous *RET* fusion-positive NSCLC, informed by data from the IAS (N=185) population from the LIBRETTO-001 trial
    - The IAS population of LIBRETTO-001 comprised *RET* fusion-positive NSCLC patients treated with selpercatinib as of the cut-off date who had received one or more lines of prior platinum-based chemotherapy (see Section B.2.3.3 for further details)

Both populations were reflective of the decision problems for each treatment line setting defined in Section B.1.1, but are narrower than the expected licensed indication for selpercatinib; as noted in Section B.1.1, the target population for this submission has been restricted to patients with non-squamous histology, which aligns with the study population for LIBRETTO-001 (both first and second line).

The analysis methodology for both populations is largely aligned, and unless otherwise stated in the sections that follow, it may be assumed the same approach has been adopted for both populations.

Subgroups

Subgroups were included to capture PD-L1 status patients who receive specific treatments which differ from the overall population, according to the NICE guidelines.

In the first line cost-effectiveness analysis, results are provided for the following two subgroups:

- PD-L1 TPS≥50%: selpercatinib versus pembrolizumab
    - Efficacy data for pembrolizumab were available in patients with PD-L1 TPS≥50% and were incorporated into the NMA (described in Section B.2.8). No data from PD-L1 subgroups were available from the LIBRETTO-001 trial, therefore the full patient population was included for selpercatinib in this subgroup analysis
- PD-L1 TPS<50%: selpercatinib versus atezolizumab combination therapy
    - Efficacy data for atezolizumab combination therapy were only available for the full population (i.e. not differentiated by PD-L1 status). Similarly, no data from PD-L1 subgroups were available from the LIBRETTO-001 trial, therefore the full patient population was included for both selpercatinib and atezolizumab combination therapy in this analysis

In the second line cost-effectiveness analysis, results are presented for the following subgroup:

- PD-L1 TPS≥1%: selpercatinib versus nivolumab and pembrolizumab
    - As described in Section B.2.8, a hierarchical exchange NMA was conducted for the second line setting, which accounted for patients' PD-L1 status, the results of which are included in this analysis. As noted above, no data from PD-L1 subgroups were available from the LIBRETTO-001 trial, therefore the full patient population informed this analysis
  - In both settings, results are additionally presented for the 'all patients' groups in each setting, reflecting comparisons with comparators for which a specified PD-L1 status is not required (vs pembrolizumab combination in first line, and nintedanib and docetaxel and atezolizumab in second line).

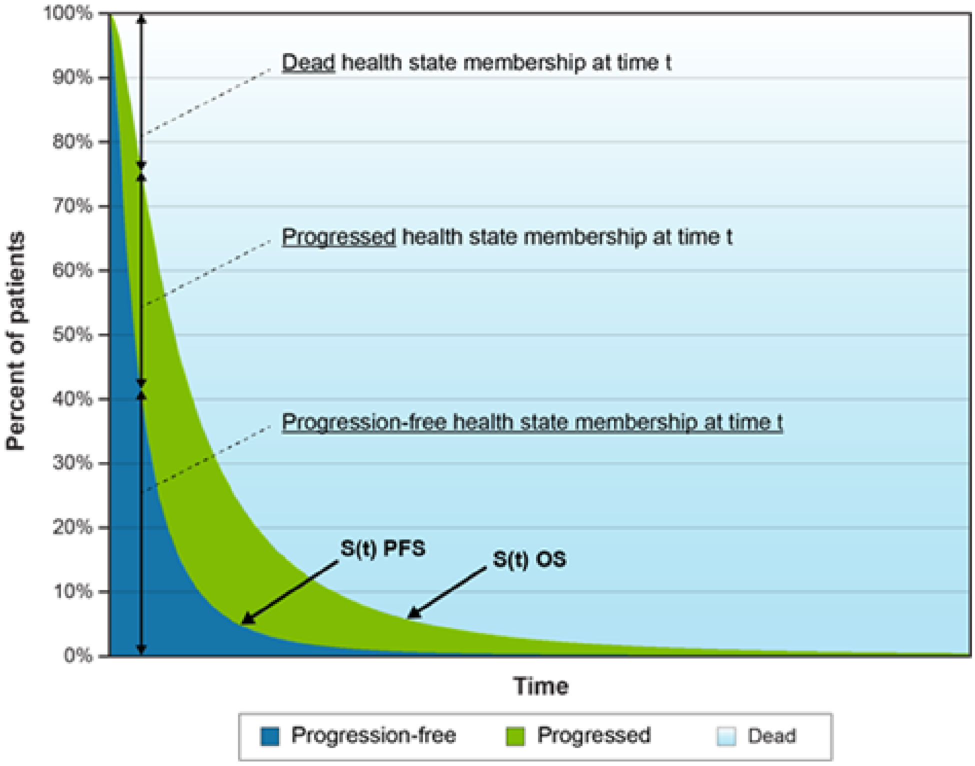
B.3.2.2 Model structure

The *de novo* cost-effectiveness model was constructed in Microsoft Excel and adopted a cohort-based partitioned survival model approach[85], in line with a number of prior NICE appraisals in NSCLC, including TA520, TA621 and TA484.[84, 86] The model was comprised of 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, administration, monitoring, medical management of the condition and the management of Grade 3/4 adverse events. 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 have subsequent anticancer therapy and incur costs associated with treatment, 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 32.

Figure 32. 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.

Cohorts of adults with *RET* fusion-positive NSCLC were modelled to enter the partitioned survival model in the progression-free health state and to receive either selpercatinib or a comparator therapy. The proportion of patients in each heath state at each model cycle was then determined for each therapy directly from cumulative survival probabilities from PFS and OS extrapolations (or PPS in the case of first line treatment, see Section B.3.3.2) for selpercatinib and relevant comparators, as follows:

- The proportion of patients occupying the progression-free state was calculated as the proportion alive and progression-free (based on PFS extrapolations)
- The proportion of patients occupying the progressed state was calculated as the proportion alive (based on OS extrapolations) minus the proportion of patients alive and progression-free (based on PFS extrapolations)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS extrapolations)
- In the first line setting, post-progression survival (PPS) was determined directly

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 and 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 *de novo* analysis

Costs and health-related 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, subsequent treatments, monitoring, health states and adverse events. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of selpercatinib versus each comparator was assessed.

In line with the NICE reference case, the analysis was conducted from the perspective of the NHS, including direct medical costs and Personal Social Services (PSS) over a lifetime time horizon from the initiation of treatment. A lifetime time horizon was chosen to be 25 years. This is similar to values chosen in recent NICE appraisals (Table 45) and was deemed reasonable based on the mean baseline age of patients in LIBRETTO-001 (61.0 years) and life expectancy for advanced NSCLC patients. A 1-week cycle length was considered in the base case, and both costs and effects were discounted at 3.5% annually.[87] Due to the short cycle length it was not deemed necessary to include a half-cycle correction. The economic analysis is conducted using the most recent estimates of resource use and treatment costs available from published sources, including NHS reference costs for 2018–2019 and the Personal Social Services Research Unit (PSSRU) costs 2019.[88, 89]

The features of the analysis were based on previous NICE appraisals including TA621, which appraised osimertinib in first line EGFR mutation-positive NSCLC, TA520, which appraised atezolizumab for locally advanced or metastatic NSCLC in the second line setting, and TA484, which appraised nivolumab for non-squamous NSCLC in the second line setting. A summary of the key features of these three appraisals and justification for the design of the *de novo* cost-effectiveness analysis for selpercatinib in first and second line NSCLC is provided in Table 45.

Table 45. Features of the economic analysis

	Previous models			Current appraisal	
Factor	**TA621**	**TA520**	**TA484**	**Chosen values**	**Justification**
Model structure	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 (25 years)	Lifetime horizon (20 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[87]
Cycle length	30 days	1 week	1 week	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	Yes	Yes	Yes	No	Due to the short length of the cycle it was not deemed necessary to include a half-cycle correction

Source of utilities	PF: 0.794; EORTC QLQ-C30 data from FLAURA trial mapped to EQ-5D.[83] PD 1L: 0.704; EORTC QLQ-C30 data from FLAURA trial mapped to EQ-5D.[83] PD 2L+: 0.640; Labbé et al. 2017.[90] ***Alternative values*** PD (≥2L): 0.678; EQ-5D-5L from AURA2 cross walked to EQ-5D-3L	EQ-5D data derived from OAK trial utilities reported as time to death rather than for PF/PF health states [86]	EQ-5D results[84] collected in CheckMate 057, PF: 0.739 PD: 0.688 ***Alternative values*** PF: 0.713 PD: 0.476 (Van Hout et al.)[91]	***1L*** PF: 0.794 PD: 0.678 (TA621; preferred values by the Committee)[83] ***2L*** PF: 0.713 PD: 0.688 (TA484; preferred values by the Committee)[84]	HSUVs used in previous NSCLC appraisals accepted by NICE were considered a relevant source of utilities, given the lack of suitable health-related quality of life trial data available for selpercatinib. Clinical expert opinion was that HSUVs from alternative forms of NSCLC would be representative of *RET* fusion-positive NSCLC
Source of costs	NHS Reference Costs PSSRU • Acquisition • Administration • Monitoring • Subsequent treatment • Testing • Health state • End of life • Adverse events • CNS metastases treatment costs	NHS Reference Costs PSSRU • Drug acquisition (comparators and subsequent treatments) • Administration • Monitoring and disease management • Terminal care • Adverse events	NHS Reference Costs PSSRU • Drug acquisition • Administration • Subsequent treatments • Monitoring • Disease management • Health states • End of life • Adverse events	NHS Reference Costs PSSRU • Drug acquisition • Administration • Subsequent treatments • Monitoring • Health states • End of life • Adverse events	Established sources of costs within the NHS. In line with the NICE reference case Costs associated with the detection of *RET* fusion-positive patients were not included in the submission due to the implementation of national genomic testing, as described in Section B.1.3.2, which would make *RET*-fusion testing, along with testing for other genetic drivers, routine.[7] Accordingly, costs for *RET* fusion testing are considered to be absorbed by the healthcare system

Abbreviations: EQ-5D: EuroQol 5-Dimensions; HSUV: health state utility values; 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.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is selpercatinib (160 mg) administered twice daily. This is in line with the proposed licensed dose for selpercatinib in *RET* fusion-positive NSCLC.[8] It is advised that treatment is administered until disease progression or unacceptable toxicity.

Comparators

First line RET fusion-positive NSCLC

As discussed previously in Section B.1.3, selpercatinib, a selective inhibitor for *RET* fusion-positive NSCLC, is a first in class therapy, and therefore there are no alternative interventions in use in the NHS in the target population. As noted in Section B.1, there are a number of first line treatment options for patients diagnosed with Stage IIIB 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 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 patients, typically have just one genetic marker, and thus would not benefit from other oncogene targeted therapies.[27, 46] 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.

As such, it is expected that selpercatinib would primarily replace pembrolizumab combination therapy (TA557)[47] in the treatment pathway in the first line setting, as this is the only therapy option currently recommended by NICE in patients with advanced NSCLC expressing no genetic or protein markers. This is supported by a market share study performed by Eli Lilly and Company for all non-squamous NSCLC treated at the first line , which found that pembrolizumab combination therapy had a market share of [redacted] in Q3 2019, giving it the highest market share of therapies recommended for cancers expressing no genetic or protein markers (Section B.1.3.2).[19]

In addition, as previously described in Section B.1.3, therapies currently recommended by NICE for the treatment of advanced NSCLC may require patients to have tumours with a specific level of PD-L1 expression. Selpercatinib may also replace other treatment options in the clinical pathway of care, including atezolizumab combination therapy (TA584),[50] recommended in patients with PD-L1 TPS<50% only, and pembrolizumab monotherapy (TA531),[49] recommended in patients with PD-L1 TPS≥50% only.[22] As discussed in Section B.1.3.2, due to superior levels of efficacy, use of immunotherapy in NHS clinical practice is largely superseding treatment with chemotherapy, as illustrated by market share data collected by Eli Lilly and Company and informed by expert clinical opinion. Accordingly, platinum-based chemotherapy is not considered a relevant comparator to selpercatinib in either the first or second line setting.

In addition to comparators recommended by NICE for the treatment of advanced NSCLC, it should be noted that pemetrexed in combination with platinum chemotherapy (carboplatin/cisplatin) was also included in the model as a reference treatment arm only, and not for the purpose of generating comparative cost effectiveness estimates versus selpercatinib. The rationale for this is that efficacy data from the pemetrexed plus platinum plus placebo arm of the KEYNOTE-189 trial were used to generate a reference arm for the LIBRETTO-001 study in the first line setting, such that comparative treatment efficacy estimates between selpercatinib and comparators relevant to the decision problem could be generated. This topic is described further in Section B.2.8.

Details of interventions included in the model for the first line treatment setting are presented in Table 46.

Table 46. Details of interventions included in the model for the first line setting

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	LIBRETTO-001 (Eli Lilly and Company Data on File)[71]
Pembrolizumab (PD-L1≥50% subgroup)	2 mg/kg	Once every 3 weeks until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation, up to a maximum of 2 years	IV	Planchard *et al.* 2018.[92]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	Pembrolizumab: 200 mg Carboplatin: AUC 5 mg/mL/min Pemetrexed: 500 mg/m^2	4 x 21-day cycles Pembrolizumab continued until 2 years and pemetrexed continued indefinitely Treatment until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	IV	Planchard *et al.* 2018;[92] TA557;[47] Langer *et al.* 2016.[93]
Atezolizumab + bevacizumab + carboplatin + paclitaxel (PD-L1<50% subgroup)[a]	Atezolizumab: 1,200 mg Bevacizumab: 15 mg/kg Paclitaxel: 200 mg/m^2 Carboplatin: AUC 6 mg/mL/min	4–6 x 21-day cycles Atezolizumab and bevacizumab continued until 2 years or progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	IV	TA584;[50] Socinski *et al.* 2012.[94]

[a] Due to the lack of data availability in PD-L1 TPS<50% patients for atezolizumab combination therapy, data from the full population were used to inform this subgroup.
Abbreviations: AUC: area under the curve; IV: intravenous; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

Second line RET fusion-positive NSCLC

Although molecular testing at Genomic Hubs should allow most patients to receive their *RET* status prior to initiating treatment for advanced NSCLC, delays may occur if initial biopsy yield is insufficient for testing or if there is a clinical need to treat the patient prior to receipt of the test result.[10] Selpercatinib may therefore be positioned as a second line treatment for those patients who received previous therapies prior to confirmation of *RET* status. Of treatments currently recommended by NICE for the treatment of advanced pre-treated NSCLC without a recognised genetic mutation, it is anticipated that selpercatinib would be administered to patients who might otherwise be treated with pembrolizumab monotherapy (TA428) and nivolumab (TA484) for patients of PD-L1 TPS>1% status, and atezolizumab monotherapy (TA520) and nintedanib in combination with docetaxel for patients of any PD-L1 TPS status. As informed by expert clinical opinion, docetaxel alone has not been included as a comparator in the analysis due to its use being largely superseded in clinical practice by nintedanib and docetaxel combination therapy. In addition, in line with the first line setting, platinum-based chemotherapies have similarly not been included due to more efficacious therapies such as immunotherapies being used more frequently in clinical practice.

As described in Section B.1.3.2, market share data collected by Eli Lilly and Company suggest that of therapies used at second line in NSCLC, atezolizumab monotherapy had the highest share in Q3 of 2019, at [redacted]. Pembrolizumab monotherapy had a market share of [redacted], followed by nintedanib combined with docetaxel ([redacted]), docetaxel monotherapy ([redacted]) and nivolumab ([redacted]). Platinum doublet chemotherapy (e.g. gemcitabine and carboplatin) had a lower market share ([redacted]), alongside pemetrexed and cisplatin ([redacted]) and pemetrexed and carboplatin ([redacted]).

In line with the approach taken for the first line setting, a treatment arm for docetaxel was also included in the model as a reference treatment arm only, and not for the purpose of generating comparative cost effectiveness estimates versus selpercatinib. The rationale for this was that efficacy data from the docetaxel plus placebo arm of the REVEL trial were used to generate a reference arm for the LIBRETTO-001 study for the second line setting, such that comparative treatment efficacy estimates between selpercatinib and comparators relevant to the decision problem could be generated. This topic is described further in Section B.2.8.

Details of interventions included in the model are summarised in Table 47.

Table 47. Details of interventions included in the model for the second line setting

Drug (patient subgroup)	Planned dosage per treatment cycle	Duration of treatment	Route	Source
Selpercatinib	160 mg, twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	Oral	LIBRETTO-001 (Eli Lilly and Company. Data on File)[71]
Nintedanib + docetaxel	Nintedanib 200 mg twice daily on days 2 to 21, in combination with docetaxel 75 mg/m^2 on day 1	In 21-day cycles until tumour progression or unacceptable AEs Standard clinical practice is to limit docetaxel to a maximum of 4 cycles per patient in the UK (ERG report, TA347)	Oral nintedanib; IV docetaxel	TA347[95]
Atezolizumab	1,200 mg	Once every 3 weeks Atezolizumab is continued until 2 years or progressive disease or unacceptable toxicity, or other reason for treatment discontinuation	IV	TA520[86]
Nivolumab (PD-L1≥1% subgroup)	3 mg/kg	Once every 2 weeks until disease progression, up to 2 years	IV	TA484[84]
Pembrolizumab (PD-L1≥1% subgroup)	2 mg/kg	Once every 3 weeks until disease progression, up to 2 years	IV	TA428[96]

Abbreviations: AE: adverse event; ERG: evidence review group; IV: intravenous; NICE: National Institute for Health and Care Excellence; NSCLC: non–small cell lung cancer; PD-L1: programmed death-ligand 1; TA: technology appraisal; UK: United Kingdom.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohorts are provided in Table 48 for first line and Table 49 for second line.

These inputs were based on the baseline characteristics of patients who received selpercatinib in the LIBRETTO-001 trial. As noted in Section B.2.3.2, the baseline characteristics of the LIBRETTO-001 trial were considered to be representative of patients in UK clinical practice.

Table 48.Patient characteristics in the model at first line

Model parameter	Value	Source
Mean age (years)	[redacted]	LIBRETTO-001 (SAS1)
Percentage female (%)	56.4	LIBRETTO-001 (SAS1)
Mean weight (kg)	[redacted]	LIBRETTO-001 (SAS1)
Mean body surface area (m^2)	1.81	TA520

Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45] NICE Technology Appraisal TA520[86].

Table 49.Patient characteristics in the model at second line

Model parameter	Value	Source
Median age (years)	61.0	LIBRETTO-001 (IAS)
Percentage female (%)	59.0	LIBRETTO-001 (IAS)
Mean weight (kg)	[redacted]	LIBRETTO-001 (IAS)
Mean body surface area (m^2)	1.81	TA520

Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off);[45] NICE Technology Appraisal TA520[86].

B.3.3.2 Survival inputs and assumptions

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 and OS (or PPS in first line). As the trial follow-up periods for the relevant interventions were shorter than the model time horizon, extrapolation from the observed OS and PFS data was required.

First line cost-effectiveness analysis

Progression-free survival

As described in Section B.2.8, a matched reference arm was generated to complement the PFS and OS data generated for selpercatinib from 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 through the application of parametric survival functions. PFS functions for other comparators relevant to the decision problem were then constructed through the application of HRs to the reference arm (pemetrexed plus platinum and placebo) extrapolation (Table 50), as generated through the first line NMA described in Section B.2.8.

Table 50. PFS HRs applied to reference arm in first line setting

Drug (Patient subgroup)	HR (95% CrI)
Pembrolizumab (PD-L1≥1% subgroup)	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]
Atezolizumab + bevacizumab + carboplatin + paclitaxel (all patients)	[redacted]

Abbreviations: CrI: Credible interval; HR: hazard ratio; PD-L1: programmed death-ligand 1; PFS: progression-free survival.

The methods for survival analysis to identify the most appropriate parametric survival functions to extrapolate the selpercatinib and reference arms followed the recommendations of NICE Decision Support Unit (DSU) TSD 14.[97] Specifically, goodness-of-fit statistics were obtained 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.

Survival functions were fitted to the selpercatinib and reference arms reconstructed from the Kaplan-Meier charts produced from the *RET*-adjustment and TMLE analyses described in Section B.2.8.

Due to the generation of extrapolations for relevant comparators 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 comparators were 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.

For the selpercatinib arm, as IPD were available to inform long-term extrapolations for PFS, it was not necessary to apply a HR to the reference arm to generate these. As such, in addition to parametric survival functions that meet the proportional hazards assumption, assessment of fit for accelerated failure time (AFT) models was also explored for the selpercatinib arm, specifically the gamma, log-normal and log-logistic functions.

In addition to the standard set of parametric functions typically explored during survival analysis, in the interest of maximising clinical and biological 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, 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 log-normal 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 in the first line setting:

- Selpercatinib arm:
  - Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, log-normal, log-logistic and gamma
  - Stratified Weibull and Gompertz, log-normal, log-logistic and gamma
  - Spline models, with one and two knots
- Reference arm (and comparators):
  - Unstratified (with treatment as an indicator variable) exponential, Weibull and Gompertz
  - Stratified Weibull and Gompertz
  - Spline models, with one and two knots

The model fit statistics for the parametric survival functions explored for selpercatinib and the reference arm for PFS in first line are presented in Table 51. The fit of the parametric survival functions to the Kaplan-Meier data for selpercatinib and the reference arm are presented in Figure 33 for PFS.

Table 51. Model fit statistics for PFS first line parametric survival functions for selpercatinib and reference arm

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Unstratified exponential	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]

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 33. PFS parametric survival functions fit versus Kaplan-Meier data for selpercatinib and reference arm in the first line setting

A. Unstratified (treatment indicator variable) functions

[redacted]

B. Stratified functions

[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; 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 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 (acknowledging the few events taking place in the selpercatinib arm).

The long-term extrapolations for each function explored for PFS in the first line setting are presented in Figure 34 for selpercatinib and Figure 35 for the reference arm.

Figure 34. Selpercatinib PFS parametric survival function extrapolations in the first line setting

[redacted]

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

Figure 35. Reference arm (pemetrexed plus platinum) PFS parametric survival function extrapolations in the first line setting

[redacted]

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

Clinical expert feedback confirmed that applying the same proportional hazards model (regardless of function choice) across treatment arms did not produce clinically feasible extrapolations. As such, model fitting was assessed for the selpercatinib and reference arms separately. Clinical expert feedback was that none of the unstratified proportional hazards or AFT functions predicted a feasible PFS estimate for selpercatinib in the long term, with the exponential, Weibull and gamma in particular providing overly optimistic estimates. Of the stratified functions, the stratified log-normal function was deemed to provide the most clinically feasible prediction. However, the clinical expert acknowledged the clinical validity of the tail for this function was uncertain due to a small proportion of patients that were assumed to remain progression free in the long term. The expert also deemed that the stratified gamma could be acceptable, but was uncertain whether the tails for selpercatinib and immunotherapy comparators would coalesce by [redacted] months, with selpercatinib crossing the pembrolizumab combination comparator arm. Therefore, the stratified lognormal was applied in the base case for selpercatinib, acknowledging this may overestimate PFS and time-on-treatment for a proportion of patients on selpercatinib.

With regards to the reference and comparator arms, the clinical expert expressed that the vast majority of extrapolations produced implausibly long PFS estimates for the reference (pemetrexed plus platinum) and comparator (immunotherapy) arms. This was likely driven by the TMLE adjustment for additional prognostic indicators to estimate the pseudo-control arm for KEYNOTE-189 (Section B.2.8). However, the fit of the reference arm was assessed against external survival data in a RET-fusion positive population and it was deemed more important the relative difference between the reference, comparator and selpercatinib arms remained clinically valid. Of all functions meeting the proportional hazards assumption, the unstratified Gompertz was deemed to produce the most clinically feasible PFS estimates for the reference arm and comparators, particularly when assessed visually against the RET-fusion-positive blended comparator Kaplan-Meier data from Flatiron (Figure 36). As such, in the base case, the stratified lognormal function was adopted for selpercatinib and the unstratified Gompertz function was adopted for the reference (pemetrexed plus platinum) and comparator (immunotherapy) arms. The influence of applying proportional hazards models across treatment arms on the cost effectiveness results are explored in scenario analyses as well as exploring the more plausible stratified gamma model for selpercatinib.

Overall survival

As presented in Section B.2.5.1, OS data from LIBRETTO-001 were very immature, with only one event in the selpercatinib arm having occurred by the cut-off date. As such, OS data were instead sourced from a set of *RET* fusion-positive patients from the Flatiron database who had progressed following first line treatment, due to the greater number of patients having experienced progression or death events available from this dataset. Survival analysis was conducted to fit parametric functions to Kaplan-Meier data obtained from this source, in line with the steps described for PFS above. Conservatively, an ‘equal PPS’ approach was adopted, whereby the same PPS estimate sourced from the Flatiron database was applied to selpercatinib, the reference arm and comparators. OS projections and therefore cost effectiveness is driven primarily by the survivor functions chosen for PFS.

A series of parametric survival functions were fitted to the matched data. The statistical goodness-of-fit test results are presented in Table 52, whilst the parametric survival extrapolations are presented against the Kaplan-Meier data from the Flatiron database in Figure 36.

Table 52. Model fit statistics for PPS parametric survival functions for Flatiron *RET* fusion-positive patients progressed after first line

Function	PPS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PPS: post-progression survival; RET: rearranged during transfection.

Figure 36. PPS parametric survival functions fit versus Kaplan-Meier data for Flatiron *RET* fusion-positive patients progressed after first line

[redacted]

Abbreviations: CI: credible interval; RET: rearranged during transfection.

The goodness-of-fit statistics suggest that there was little difference between functions in terms of statistical fit to the Kaplan-Meier data, although the AIC and BIC rankings were consistent for both statistics, with the exponential ranking highest in both cases. Upon inspection of visual fit, all five functions demonstrated a reasonable fit to the Kaplan-Meier data, all slightly underestimating PFS around the 12-month timepoint. Based on best statistical fit, the exponential form was selected for the base case. Scenario analyses based on extrapolation of trial data was explored for proportional hazards models fitted across all the treatment arms.

The base case extrapolations for selpercatinib and comparators are presented in Figure 37 for PFS and Figure 38 for OS (incorporating PFS and PPS) for the first line setting.

Figure 37. Base case extrapolations for selpercatinib and comparators for first line PFS

A. All patients

[redacted]

Footnotes: The selpercatinib and pemetrexed plus platinum Kaplan-Meier data having undergone adjustment for *RET* fusion and TMLE are presented. 'Plot data' represent first line PFS data for first line RET-fusion positive patients from the Flatiron CGDB.
Abbrevations: KM: Kaplan-Meier; PD-L1: programmed death-ligand 1; Pem + Plat: pemetrexed plus platinum; Pembro + Pem + Plat: pembrolizumab + pemetrexed plus platinum

B. PD-L1≥50%

[redacted]

Footnotes: The selpercatinib and pemetrexed plus platinum Kaplan-Meier data having undergone adjustment for *RET* fusion and TMLE are presented. 'Plot data' represent first line PFS data for first line *RET* fusion-positive patients from the Flatiron CGDB.
Abbrevations: KM: Kaplan-Meier; PD-L1: programmed death-ligand 1 Pem + Plat: pemetrexed plus platinum; Pembro + Pem + Plat: pembrolizumab + pemetrexed plus platinum

C. PD-L1<50%

[redacted]

Footnotes: The selpercatinib and pemetrexed plus platinum Kaplan-Meier data having undergone adjustment for *RET* fusion and TMLE are presented. 'Plot data' represent first line PFS data for first line RET-fusion positive patients from the Flatiron CGDB.

Abbrevations: KM: Kaplan-Meier; PD-L1: programmed death-ligand 1; Pem + Plat: pemetrexed plus platinum; Pembro + Pem + Plat: pembrolizumab + pemetrexed plus platinum.

Figure 38. Base case extrapolation for selpercatinib and comparators for OS (incorporating PFS and PPS) following first line treatment

A. All patients

[redacted]

B. PD-L1 ≥50% subgroup

[redacted]

C. PD-L1 <50% subgroup

[redacted]

Abbreviations: PD-L1: programmed death-ligand 1; PPS: post-progression survival.

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OS-PFS surrogate scenario analysis

Due to the immaturity of OS data available from LIBRETTO-001, a scenario analysis was conducted whereby PFS data for selpercatinib were utilised as a surrogate for OS. Within this scenario, the difference in median OS for selpercatinib versus the reference arm (pemetrexed plus platinum) was estimated based on the difference in median PFS (estimated from the base case PFS function: stratified log-normal) and a regression analysis for the association between PFS and OS in first line advanced NSCLC conducted by Pfeiffer et al.[98] OS for selpercatinib was estimated by applying the median OS difference to the median OS for the reference arm. This scenario was conducted to explore uncertainty around OS for selpercatinib. For comparators, available OS data are utilised (i.e. OS HR data obtained through the NMA [Section B.2.8] are applied to the reference arm). The results of this scenario are presented in Section B.3.8.3.

Second line cost-effectiveness analysis

Survival estimation for the second line *RET* fusion-positive NSCLC population followed the same methodology and process as the first-line population. Instead, utilising a reference arm of docetaxel plus placebo, based on data from the REVEL trial (described further in Section B.2.8).

Similarly to the first line analysis, in order to inform long-term estimates of PFS and OS in the model for selpercatinib and comparators, it was necessary to extrapolate the PFS and OS data generated for selpercatinib and the reference arm (docetaxel plus placebo) through the use of parametric survival functions. Survival functions for other comparators relevant to the decision problem were constructed through the application of HRs generated for each comparator in the NMA (described in Section B.2.8) to the reference arm extrapolation (Table 53). The exception to this was for atezolizumab, where no second line data were available for PFS. Data for OS from clinical trials indicate that atezolizumab is similar in efficacy to nivolumab (OS HR for nivolumab [all patients] versus atezolizumab = 1.06 [95% CrIs: 0.48–2.36]).[58] Therefore, the PFS HR for atezolizumab was assumed to be the same as the HR generated for nivolumab (across the full patient population, rather than the PD-L1≥1% subgroup).

Table 53. HRs applied to reference arm in second line setting

Drug (Patient subgroup)	PFS	OS
Nintedanib + docetaxel	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Nivolumab (all patients)	[redacted]	[redacted]
Nivolumab (PD-L1–positive subgroup)	[redacted]	[redacted]
Pembrolizumab (PD-L1–positive subgroup)	[redacted]	[redacted]

[redacted]

Abbreviations: HR: Hazard radtio; NA: not applicable: OS: overall survival; PD-L1: programmed death PFS: progression-free survival;

Progression-free survival

The model fit statistics for the parametric survival functions explored for selpercatinib and the reference arm for PFS in second line are presented in Table 54. The fit of the parametric survival functions to the Kaplan-Meier data for selpercatinib and the reference arm are presented in Figure 39 for PFS.

Table 54. Model fit statistics for PFS second line parametric survival functions for selpercatinib and reference arm

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 39. PFS parametric survival functions fit versus Kaplan-Meier data for selpercatinib and reference arm in the second line setting

(A) Unstratified (treatment indicator variable) functions

[redacted]

(B) Stratified functions

[redacted]

Abbreviations: AIC: akaike information criterion; BIC: Bayesian information criterion; HR: hazard ratio; NSCLC: non–small cell lung cancer; PFS: progression-free survival;RET: rearranged during transfection.

As with the first line analysis, according to AIC/BIC statistics, all survival functions have similar fits to the observed Kaplan-Meier data for both the selpercatinib and reference arms. This is reflected in the visual assessment of the fit of functions to the Kaplan-Meier data, which all appear to provide a similar fit to both arms.

The long-term extrapolations for each function explored for PFS in the second line setting are presented in Figure 40 for selpercatinib and Figure 44 for the reference arm.

Figure 40. Selpercatinib PFS parametric survival function extrapolations in the second line setting

[redacted]

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

Figure 41. Reference arm (docetaxel) PFS parametric survival function extrapolations in the second line setting

[redacted]

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

Similarly to the first line analysis, feedback from the clinical expert was that the adjustment made to the docetaxel reference arm through application of the time acceleration factor and TMLE had resulted in overly optimistic estimations for the chemotherapy-based reference arm. As a result, overly optimistic predictions for comparators (i.e. immunotherapies) would be likely be predicted following the application of HRs from the NMA. However, unlike the first line analysis, the relative difference was substantial between the reference and selpercatinib arms (Section B.2.8). Accordingly, the expert's choice of the most clinically plausible extrapolation took this factor into account. As with the first line process, proportional hazards models fitted across all treatment arms were first explored, and it was deemed that separate models fitted to the selpercatinib and the reference (docetaxel) (and comparators [immunotherapies]) arms would produce more plausible estimates. As such, suitable models were chosen for the reference (docetaxel) (and comparator) arms to offset overestimation of PFS. Therefore, the stratified gamma was selected for the base case selpercatinib extrapolation, whilst the Weibull function was selected as the most clinically plausible extrapolation for the reference arm and comparators. A visual assessment of the reference and comparator extrapolations to the *RET* fusion-positive Kaplan-Meier dataset from the Flatiron database showed that PFS was still overestimated for comparators, but the relative difference between arms was more clinically plausible. The influence of applying proportional hazards models across treatment arms on the cost-effectiveness results are explored in scenario analyses.

Overall survival

Unlike the first line setting, the availability of more mature data for selpercatinib in the second line setting negated the requirement to utilise the 'equal PPS' approach, although this approach is explored for second line in a scenario analysis.

The model fit statistics for the parametric survival functions explored for selpercatinib and the reference arm for OS in second line are presented in Table 55. The fit of the parametric survival functions to the Kaplan-Meier data for selpercatinib and the reference arm are presented in Figure 42 for OS.

Table 55. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=3	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Stratified log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival

Figure 42. OS parametric survival functions fit versus Kaplan-Meier data for selpercatinib and reference arm in the second line setting

(A) Unstratified (treatment indicator variable) functions

[redacted]

(B) Stratified functions

[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; HR: hazard ratio; NSCLC: non–small cell lung cancer; OS: overall survival.

As with the first line analysis, according to AIC/BIC statistics, all survival functions have similar fits to the observed Kaplan-Meier data for both the selpercatinib and reference arms. This is reflected in the visual assessment of the fit of functions to the Kaplan-Meier data, which all appear to provide a similar fit to both arms.

The long-term extrapolations for each function explored for OS in the second line setting are presented in Figure 43 for selpercatinib and Figure 44 for the reference arm.

Figure 43. Selpercatinib OS parametric survival function extrapolations in the second line setting

[redacted]

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

Figure 44. Reference arm (docetaxel) OS parametric survival function extrapolations in the second line setting

[redacted]

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

As with the assessment of PFS, feedback from the clinical expert confirmed that OS may be overestimated due to the application of the time acceleration factor and TMLE. This was more evident for the comparator (immunotherapy) arms than the reference (docetaxel) arm, when the application of the same proportional hazards models across treatment arms were utilised. As such, separate models were fitted to the selpercatinib arm and reference (and comparator) arms. The unstratified exponential and unstratified Weibull for the selpercatinib and reference (and comparator) arms, respectively, were deemed to be the most clinically plausible functions. The influence of applying proportional hazards models across all treatment arms on the cost-effectiveness results are explored in scenario analyses.

The base case extrapolations for selpercatinib and comparators are presented in Figure 45 for PFS and Figure 46 for OS for the second line setting.

Figure 45. Base case extrapolations for selpercatinib and comparators for second line PFS

A. All patients

[redacted]

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

B. PD-L1≥1% subgroup

[redacted]

Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death-ligand 1.

Figure 46. Base case extrapolations for selpercatinib and comparators for second line OS

A. All patients

[redacted]

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

B. PD-L1 ≥1% subgroup

[redacted]

Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death-ligand 1..

B.3.3.3 Time to treatment discontinuation

In line with the methodology described in Section B.3.3.2 and in accordance with the NICE DSU TSD14, a range of standard parametric distributions were explored for extrapolation of time to treatment discontinuation (TTD) data from the LIBRETTO-001 trial in order to estimate duration of treatment for selpercatinib and are presented in Appendix J. However, for the first line and second line setting, TTD for selpercatinib was assumed to be the same as PFS due to the PFS extrapolation demonstrating greater clinical validity than the parametric survival extrapolations for TTD. Treatment discontinuation for comparators was similarly modelled to align with PFS, capped at a maximum number of cycles where specified, see Table 46, Section B.3.2.3.

B.3.3.4 Adverse events

Probabilities of individual adverse events for each intervention were based on trial data. Grade 3–4 adverse events with at least 2% difference in frequency between interventions were included. Costs and utility decrements (if any) associated with each adverse event were included in the model, see Section B.3.4.4 and B.3.5.3, respectively. The incidence of Grade 3–4 adverse events included in the model for selpercatinib and comparators are reported in Table 56 and Table 57 for the first and second line populations, respectively.

Table 56: Incidence of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model, first line treatment

Adverse event	Selpercatinib	Pembrolizumab	Pembrolizumab + pemetrexed + carboplatin/cisplatin	Atezolizumab + bevacizumab + carboplatin + paclitaxel
Diarrhoea	[redacted]	3.90%	5.19%	2.80%
Hypertension	[redacted]	0.00%	0.49%	6.36%
ECG QT prolonged	[redacted]	0.00%	0.00%	0.00%
Abdominal pain	[redacted]	0.00%	0.00%	0.00%
Fatigue	[redacted]	1.30%	5.68%	3.31%
Decreased appetite	[redacted]	0.00%	1.48%	2.54%
Asthenia	[redacted]	0.00%	6.17%	1.27%
Vomiting	[redacted]	0.65%	3.70%	1.53%
Dyspnoea	[redacted]	0.65%	3.70%	0.00%
Alanine aminotransferase increased	[redacted]	1.30%	0.00%	0.00%
Aspartate aminotransferase increased	[redacted]	0.65%	0.00%	0.00%
Hyponatraemia	[redacted]	2.60%	0.25%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%	0.00%
Pneumonia	[redacted]	1.95%	5.68%	0.00%
Thrombocytopenia	[redacted]	0.00%	7.90%	4.07%
Neutropenia	[redacted]	0.00%	15.80%	13.74%
Anaemia	[redacted]	1.95%	16.30%	6.11%
Pleural effusion	[redacted]	3.25%	1.48%	0.00%
Febrile neutropenia	[redacted]	0.00%	5.68%	9.16%
Pneumonitis	[redacted]	2.60%	2.96%	0.76%
Nausea	[redacted]	0.00%	3.46%	3.82%
Hepatitis Lab abnormalities	[redacted]	0.00%	1.48%	3.05%
Sepsis	[redacted]	1.30%	1.98%	0.00%

Acute kidney injury	[redacted]	0.00%	1.98%	0.00%
Chronic obstructive pulmonary disease	[redacted]	2.60%	0.99%	0.00%
Urinary tract infection	[redacted]	0.65%	0.99%	0.00%
Peripheral neuropathy	[redacted]	0.00%	0.00%	2.80%
Decreased platelet count	[redacted]	0.00%	0.25%	5.09%
Decreased neutrophil count	[redacted]	0.00%	0.00%	8.65%
Severe skin reaction	[redacted]	3.90%	0.00%	0.00%
Proteinuria	[redacted]	0.00%	0.00%	2.54%
Source:	LIBRETTO-001[71]	KEYNOTE-042[99]	KEYNOTE-189[67]	Impower150[94]

Abbreviations: ECG: Electrocardiogram

Table 57: Incidence of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model, second line treatment

Adverse event	Selpercatinib	Nintedanib + docetaxel	Atezolizumab	Nivolumab	Pembrolizumab	Docetaxel
Diarrhoea	[redacted]	6.60%	0.66%	0.70%	0.59%	3.07%
Hypertension	[redacted]	0.00%	0.00%	0.00%	0.00%	2.10%
ECG QT prolonged	[redacted]	0.00%	0.00%	0.00%	0.00%	0.00%
Haemorrhage	[redacted]	0.15%	0.33%	0.00%	0.88%	2.27%
Fatigue	[redacted]	5.67%	0.33%	1.05%	1.18%	10.52%
Decreased appetite	[redacted]	1.38%	0.33%	0.00%	0.88%	1.29%
Asthenia	[redacted]	2.30%	1.31%	0.35%	0.29%	0.00%
Dyspnoea	[redacted]	4.91%	2.46%	3.14%	1.77%	8.25%
Alanine aminotransferase increased	[redacted]	7.82%	0.16%	0.00%	0.29%	0.00%
Aspartate aminotransferase increased	[redacted]	3.37%	0.16%	0.00%	0.29%	0.00%
Hyponatraemia	[redacted]	2.15%	0.16%	0.35%	0.29%	0.00%

Lymphopenia	[redacted]	0.00%	0.00%	0.00%	0.00%	0.00%
Pneumonia	[redacted]	3.07%	3.28%	4.18%	4.42%	0.00%
Thrombocytopenia	[redacted]	0.00%	0.00%	0.00%	0.00%	0.65%
Neutropenia	[redacted]	12.12%	0.49%	0.00%	0.00%	39.81%
Anaemia	[redacted]	1.07%	2.30%	0.35%	0.88%	5.66%
Pleural effusion	[redacted]	1.23%	1.81%	2.79%	1.18%	0.00%
Febrile neutropenia	[redacted]	7.06%	0.16%	0.00%	0.29%	10.03%
Urinary tract infection	[redacted]	0.15%	0.00%	0.35%	0.00%	0.00%
Decreased neutrophil count	[redacted]	32.06%	0.00%	0.35%	0.00%	0.00%
Decreased white blood cell count	[redacted]	16.41%	0.00%	0.00%	0.00%	0.00%
Leucopenia (Leukopenia)	[redacted]	2.91%	0.00%	0.00%	0.00%	12.46%
Stomatitis	[redacted]	0.15%	0.00%	0.00%	0.00%	1.62%
Neuropathy	[redacted]	0.00%	0.00%	0.00%	0.00%	1.62%
Mucosal inflammation	[redacted]	0.15%	0.00%	0.00%	0.00%	0.49%
Venous thromboembolic	[redacted]	0.15%	0.16%	0.35%	0.00%	2.91%
General malaise	[redacted]	0.15%	0.00%	0.00%	0.00%	0.00%
Infection	[redacted]	0.00%	0.00%	0.35%	0.00%	0.00%
Paranychia	[redacted]	0.00%	0.00%	0.00%	0.00%	0.00%
Malignant neoplasm progression	[redacted]	3.83%	0.00%	8.01%	0.00%	0.00%
Pulmonary embolism	[redacted]	0.61%	1.48%	3.83%	2.36%	0.00%
Respiratory failure	[redacted]	1.23%	0.49%	2.09%	0.59%	0.00%
Source:	LIBRETTO-001[71]	LUME-Lung 1[82]	OAK[100]	CheckMate057[76]	KEYNOTE-010[101]	REVEL[72]

Abbreviations: ECG: Electrocardiogram.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 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.2.5.3 for patients with *RET* fusion-positive NSCLC treated with selpercatinib. The questionnaires were to be answered by the subject to the best of his/her ability, prior to receiving drug on the first day of treatment, at the start of each 4-weekly treatment cycle (within 7 days of each subsequent radiologic assessment, preferably prior to learning the results of the radiologic disease assessment), and at the end of treatment visit. Therefore, few data were collected for patients in the progressed health state due to the small number of patients with progressive disease in the LIBRETTO-001 trial.

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

B.3.4.2 Mapping

Given that EORTC QLQ-C30 data were collected in LIBRETTO-001, the possibility of mapping such data to the EQ-5D to potentially capture health-related quality of life in *RET* fusion-positive patients was explored. The beta-binomial model provided in the mapping study by Khan et al.[102] was originally chosen to conduct the mapping exercise, as it was found to offer the best fit for the EQ-5D-3L. However, the resulting baseline utility value from the mapping exercise was found to substantially lack clinical plausibility, resulting in a value of 0.9984. Accordingly, the random effects linear regression models provided by Khan et al. were also explored. However, this model also resulted in unrealistic baseline estimates for utility of approximately 0.99. Accordingly, mapped utility values were not used to inform the cost-effectiveness analysis.

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

In the first line population, utility values included in the model were based on values from a targeted literature review of previous technology appraisals that had been accepted by NICE. Therefore, no further extraction of HRQoL studies from the SLR to identify cost-effectiveness studies was performed.

To identify studies relevant to patients receiving treatments at second line, an SLR was conducted to identify relevant HRQoL and utility data relevant to the cost-effectiveness analysis. Details of the SLR search strategy are presented in Appendix H. No estimates specific to patients with *RET* fusion-positive tumours were identified. Accordingly, in line with the approach taken for the first line setting, a targeted literature review of recent relevant NICE appraisals was used to identify data that have been accepted by NICE, as described in Section 0.

B.3.4.4 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 B.1.3. 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, is in line with previous cost-effectiveness analyses in NSCLC.

As described above, no appropriate utility data could be elicited from LIBRETTO-001, therefore utility decrements for adverse events and associated duration in the first and second line setting 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 58 and Table 59 for the first and second line cost effectiveness analyses, respectively.

Table 58: Adverse event disutility decrements applied in the cost-effectiveness model for first line treatment

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	-0.090	15.0	-0.0037	Assumed same as Febrile Neutropenia
Acute kidney injury	-0.085	15.0	-0.0035	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	-0.085	15.0	-0.0035	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 Excelence.
Source: Doyle et al., 2008;[103] KEYNOTE-010 (TA428);[101] Marti et al., 2013;[104] Nafees et al., 2008;[105] NICE TA306;[106] NICE TA428;[96]
NICE TA476;[107]; NICE TA484;[84] NICE TA621.[83]

Table 59: Disutility decrements applied in the cost-effectiveness model, second line treatment

Adverse event	Decrement	Duration (days)	QALY loss	Source
Diarrhoea	-0.0468	5.5	-0.0007	Decrement: NICE TA484; Duration: NICE TA476 (Study CA046)
Hypertension	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
ECG QT prolonged	0.0000	0.0	0.0000	Decrement: Assumption
Haemorrhage	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Fatigue	-0.0735	23.8	-0.0048	Decrement: NICE TA484; Duration: NICE TA306

Decreased appetite	-0.0850	15.0	-0.0035	Decrement: NICE TA428 (KEYNOTE-010); Duration: Assumption
Asthenia	-0.0735	23.8	-0.0048	Decrement: NICE TA484; Duration: Assumption (same as fatigue)
Dyspnoea	-0.0500	15.0	-0.0021	Decrement: NICE TA484; Duration: Assumption
Alanine aminotransferase increased	-0.0500	14.7	-0.0020	Decrement: NICE TA484; Duration: Assumption
Aspartate aminotransferase increased	0.0000	14.7	0.0000	Decrement: NICE TA484; Duration: Assumption
Hyponatraemia	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Lymphopenia	-0.0500	15.0	-0.0021	Decrement: NICE TA484; Duration: Assumption
Pneumonia	-0.0080	15.0	-0.0003	Decrement: NICE TA484; Duration: Assumption
Thrombocytopenia	0.0000	0.0	0.0000	Decrement: Assumption; Duration:
Neutropenia	-0.0897	15.0	-0.0037	Decrement: NICE TA484; Duration: Assumption
Anaemia	-0.0735	23.8	-0.0048	Decrement: NICE TA484; Duration: Assumption (same as fatigue)
Pleural effusion	0.0000	15.0	0.0000	Decrement: NICE TA484; Duration: Assumption
Febrile neutropenia	-0.0900	15.0	-0.0037	Decrement: NICE TA484; Duration: Assumption
Urinary tract infection	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Decreased neutrophil count	0.0000	0.0	0.0000	Decrement: NICE TA484; Duration: Assumption
Decreased white blood cell count	-0.0500	15.0	-0.0021	Decrement: NICE TA484; Duration: Assumption
Leucopenia (Leukopenia)	-0.0897	15.0	-0.0037	Decrement: NICE TA484; Duration: Assumption
Stomatitis	-0.0850	15.0	-0.0035	Decrement: NICE TA428 (KEYNOTE-010); Duration: Assumption
Neuropathy	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption

Mucosal inflammation	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Venous thromboembolic	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
General malaise	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Infection	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Paranychia	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Malignant neoplasm progression	0.0000	0.0	0.0000	Decrement: Assumed included in progressed health state
Pulmonary embolism	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption
Respiratory failure	-0.0850	15.0	-0.0035	Decrement: NICE TA428; Duration: Assumption

Abbreviations: ECG: Electrocardiogram; QALY: quality-adjusted life year; NICE; National Institue for Health and Care Excelence.
Source: KEYNOTE-010;[101] NICE TA428;[96] NICE TA476;[107] NICE TA484.[84]

B.3.4.5 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.

In the base case analysis HSUVs differed among the first line and second line patient populations but did not differ between treatment arms due to the lack of control arm and lack of HRQoL data collected from LIBRETTO-001. For the first line population, HSUVs were assumed to align with those accepted for TA621 for osimertinib in untreated EGFR mutation-positive NSCLC, 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.

For the second line population, a different set of HSUVs was considered to the first line population, given these patients are in worse health having progressed following prior treatment. HSUVs sourced from TA484 were considered to be a suitable proxy since patients had progressed following prior chemotherapy. Plausible HSUVs determined by the Committee from TA484 were applied using the upper limit of its preferred values (0.68). The lower limit was not considered suitable (0.476) since this value was based on an older study by Van Hout et al. (2006) in patients receiving palliative chemotherapy. Patients now have considerably more options at second line and following progression to third line treatment. It is acknowledged the PD value is uncertain, particularly as it similar to the PD value used for first-line patients. Therefore, additional HSUVs values were explored in scenario analyses to determine the impact on the cost effectiveness of selpercatinib, detailed in Table 60.

Table 60: Utility estimates for first and second line NSCLC

Scenario	HSUVs	Source	Justification
First line			
Base case	PF: 0.794 PD:0.678	TA621	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
1	PF: 0.784 PD: 0.517	TA310 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
2	PF: 0.814 PD non-CNS: 0.725	TA536 PF and PD: ALEX	ALK treatment considered a suitable proxy for selpercatinib. Direct elicitation of EQ-5D data from the pivotal trial
3	PF: 0.71 PD: 0.67	Chouiad et al. 2013	Utility values for patients with advanced NSCLC on first line treatment or progressed while on first line treatment
Second line			
Base case	PF: 0.713 PD: 0.688	TA484	Considered a suitable proxy for selpercatinib since patients had progressed following prior chemotherapy
1	PF: 0.853 PD: 0.659	TA416 AURA2	EGFR-treatment considered a suitable proxy for selpercatinib. Utility values elicited directly from trial data and specific to second line treatment and patients progressed and receiving ≥third-line treatment.
2	0.672 PD: 0.6532–0.1798 (0.473)	TA310 Nafees et al. 2008	Nafees et al. looked specifically at HSUVs for patients on second-line treatment
3	PF: 0.687 PD: 0.64	TA416 LUME-Lung 1	Values preferred by the ERG for patients progressing after first line treatment on crizotinib. LUME-Lung 1 study was in patients receiving second line nintedanib plus docetaxel

Abbreviations: ALK: Anaplastic lymphoma kinase; HSUVs: health state utility values; PD: progressed disease; PF: progression-free; NSCLC: non-small cell lung cancer; SE: standard error; TA: technology assessment; EGFR: ERG: evidence review group.
Source: TA621;[83] TA310; [108] TA536; [109]
TA484;[84] TA416;[110] Nafees et al. 2008; [105] LUME-Lung 1;[82]

Clinical expert opinion verified that the estimates are reasonable for patients with *RET*-altered tumours, at both first and second line, and that HRQoL in this population may be expected to be similar to that of the wider patient population with the same tumour type.

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

In the first line population, 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.

In the second line population, an SLR was conducted to identify any relevant cost and healthcare resource use data associated with the treatment of adults with *RET* fusion-positive NSCLC at the second line. Details of the SLR search strategy and study selection can be found in Appendix I. The SLR identified previous technology appraisals as the primary source of data for the second line population.

The following resource use categories were captured in the analysis:

- Section B.3.5.1: drug acquisition and administration costs treatment cost for first and second line treatments
- Section B.3.5.2: Health state unit costs and resource use
- Section B.3.5.3: AE costs and resource use
- Section B.3.5.4: End of life costs

As per Section B.3.2.2, the perspective is that of the UK NHS and PSS. Drug costs for all interventions were primarily sourced from the electronic market information tool (eMIT) or the British nation formulary (BNF)

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs for selpercatinib and relevant comparators were based on their list price and all prices were extracted from the British National Formulary (BNF) online (2020) or electronic market information tool (eMIT; 2019) for generic comparators. List prices included in the cost-effectiveness analysis are presented in Table 61 and **Source:** BNF (2020)[59]; eMIT[66]; Eli Lilly and Company. Data on file.[71]

Table 62 for the first and second line analysis, respectively. For adjusted-dose interventions a body weight estimate of 72 kg and a body surface area of 1.81 m^2 were used for both treatment line settings.

Table 61: Drug acquisition costs for selpercatinib and relevant comparators in the first line setting

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)	Source
Selpercatinib	Capsules	80 mg	60	[redacted]	Eli Lilly and Company. Data on file.
Selpercatinib	Capsules	40 mg	60	[redacted]	Eli Lilly and Company. Data on file.
Pembrolizumab	Vial	25 mg/ml	4 ml	2630.00	BNF (2020)
Pembrolizumab + pemetrexed + carboplatin					

Pembrolizumab	Vial	25 mg/ml	4 ml	2630.00	BNF (2020)
Pemetrexed	Powder	100mg	1	160.00	BNF (2020)
Carboplatin	Vial	10 mg/ml	45 ml	7.40	eMIT (2019)
Atezolizumab + bevacizumab + carboplatin + paclitaxel					
Atezolizumab	Vial	60 mg/ml	20 ml	3807.69	BNF (2020)
Bevacizumab	Vial	25 mg/ml	16	924.40	BNF (2020)
Carboplatin	Vial	10 mg/ml	45 ml	18.78	eMIT (2019)
Paclitaxel	Vial	6 mg/ml	16.67 ml	200.35	BNF (2020)

Source: BNF (2020)[59]; eMIT[66]; Eli Lilly and Company. Data on file.[71]

Table 62: Drug acquisition costs for selpercatinib and relevant comparators in the second line setting

Treatment	Form	Strength/Unit	Pack size	Cost per pack (£)	Source
Selpercatinib	Capsules	80 mg	60	[redacted]	Eli Lilly and Company. Data on file.
Selpercatinib	Capsules	40 mg	60	[redacted]	Eli Lilly and Company. Data on file.
Pembrolizumab	Vial	25 mg/ml	4 ml	2630.00	BNF (2020)
Nivolumab	Vial	10 mg/ml	4 ml	439.00	BNF (2020)
Nintedanib + docetaxel					
Nintedanib	Capsules	100 mg	60, 120	2151.10	BNF (2020)
Docetaxel	Vial	160 mg/ml	8 ml	16.80	eMIT (2019)
Atezolizumab	Vial	60 mg/ml	20 ml	3807.69	BNF (2020)

Source: BNF (2020)[59]; eMIT[66]; Eli Lilly and Company. Data on file.[71]

The mean dose intensity observed in the LIBRETTO-001 trial ([redacted]%) was used to account for dose reductions and any treatment breaks for both the first and setting line settings. Given RDI data were not available for comparators, conservatively, the same RDI was used for selpercatinib and comparators. The final dose reduction levels are yet undetermined for selpercatinib. Some patients in the LIBRETTO-001 trial, and in practice as determined by the final SmPC, may have had doses reduced beyond 120 mg, which would impact treatment cycle costs, and thus costs may be overestimated for selpercatinb in the model.

Treatment discontinuation for comparators was modelled using the PFS curve for the intervention, capped at a maximum number of cycles where specified.

In the base case, drug wastage was not included for oral drugs. For IV drugs, it is assumed that unused treatment in open vials are discarded. The weight and BSA distribution of the population is modelled and the lowest cost vial combination is determined according to each weight or BSA category. The cost of each whole vial combination is calculated and the weighted average cost across the population is calculated using the proportion of patients in each weight or BSA category.

Table 63: Treatment costs included in the first line 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 (2 mg/kg, every 3 weeks, IV)[b]	3	5282.39	4745.35			Dose=ESMO (Planchard et al., 2018) Dose intensity assumed same as selpercatinib
Pembrolizumab + pemetrexed + carboplatin[c]	3	6748.76	5761.29	5740.66	1243.36	Dose=NICE TA584; Socinski et al. (2012) Dose intensity assumed same as selpercatinib
Pembrolizumab (200 mg, every 3 weeks, IV), up to 2 years		5260.00	4497.30	4497.30	0.00	
Pemetrexed (500 mg/m^2, every 3 weeks, IV)		1465.33	1243.36	1243.36	1243.36	
Carboplatin (5 mg/ml, every 3 weeks, IV) for up to 4 treatment cycles		23.43	20.63	0.00	0.00	
Atezolizumab + bevacizumab + carboplatin + paclitaxel[d]	3	7257.75	6229.96	5564.79	0.00	Dose=NICE TA584; Socinski et al. (2012)

Atezolizumab (1200 mg, every 3 weeks, IV), up to 2 years		3807.69	3255.57	3255.57	0.00	Dose intensity assumed same as selpercatinib
Bevacizumab (15 mg/kg, every 3 weeks, IV), up to 2 years		2678.43	2309.22	2309.22	0.00	
Carboplatin (6 AUC, every 3 weeks, IV), up to 6 treatment cycles		27.57	23.95	0.00	0.00	
Paclitaxel (200 mg/m^2, every 3 weeks, IV), up to 6 treatment cycles		744.07	641.22	0.00	0.00	

Notes: [a] Period 1: Week 0–3; Period 2: Week 4+ [b] Period 1: week 0–2; Period 2: week 3+ [c] Period 1: Week 0–2; Period 2: Week 3–11; Period 3: Week 12–103; Period 4: Week 104+ [d] Period 1: Week 0–2; Period 2: Week 3–17; Period 3: Week 18–103; Period 4: Week 104+
Abbreviations: IV: intravenous; NICE: National Institute for Health and Care Excellence.
Source: Draft SmPC; Eli Lilly and Company. Data on file.[71]; NICE TA584;[50] Planchard et al., 2018;[92] Socinski et al. (2012)[94]

Table 64: Treatment costs included in the second line 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
Atezolizumab (1200 mg, every 3 weeks, IV), up to 2 years[b]	3	3807.69	3255.57	-	-	Dose=NICE TA520 Dose intensity=assumed same as selpercatinib

Nivolumab (3 mg/kg, every 2 weeks, IV), up to 2 years[c]	2	2338.44	2015.34	-	-	Dose=NICE TA484 Dose intensity=assumed same as selpercatinib
Pembrolizumab (2 mg/kg, every 3 weeks, IV), up to 2 years[d]	3	5022.45	4445.00	0.00	-	Dose=NICE TA428 Dose intensity=assumed same as selpercatinib
Nintedanib + Docetaxel[e]	3	1528.65	1526.62	1505.77	-	Dose=NICE TA347
Nintedanib (200 mg twice daily, oral)		1505.77	1505.77	1505.77		Dose intensity=assumed same as selpercatinib
Docetaxel (75 mg/m^2, every 3 weeks, IV), up to 4 cycles		22.88	20.85	0.00		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+ [c] Period 1: week 0–1; Period 2: week 2+ [d] Period 1: Week 0–2; Period 2: Week 3–103; Period 3: Week 104+ [e] Period 1: Week 0–2; Period 2: Week 3–11; Period 3: Week 12+
Abbreviations: IV: intravenous; NICE: National Institute for Health and Care Excellence.
Source: Draft SmPC; Eli Lilly and Company. Data on file.[71]; NICE TA484;[84] NICE TA347;[95] NICE TA520;[86] TA428.[96]

Administration costs

Administration costs were based on NHS Reference Costs. For selpercatinib and other oral drugs, 12 minutes of pharmacy time was assumed every 30 days. Additional drug administration costs for IV drug administration were taken from relevant TAs, as summarised in Table 65 for the first line cost-effectiveness analysis and Table 66 for the second line cost-effectiveness analysis. During treatment, patients were assumed to have one oncologist visit every 3 weeks; the visit costs are converted to an average weekly cost and applied each model cycle while a patient is progression-free. In the base case for the first and second line cost-effectiveness analysis, a mean cost of £64.67 (SE: 6.47; £58.20–71.13) was applied.

Table 65: Drug administration costs for selpercatinib and comparators in the first line setting

Treatment	Mean cost, £	SE	Lower bound	Upper bound	Source
Selpercatinib	9.20	0.92	7.40	11.00	NICE TA520; PSSRU 2019 Table 9 Band 6 hourly wage (12min pharmacy time)
Pembrolizumab	185.00	18.50	148.74	221.26	NICE TA 520; NHS 2018/19 SB12Z Outpatient (30min IV infusion)
Pembrolizumab + pemetrexed + carboplatin	502.73	50.27	404.19	601.27	NICE TA 557; NHS 2018/19 SB12Z + SB14Z Outpatient (30min+10min+15min IV infusion)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	385.28	38.53	309.77	460.79	NICE TA 584; NHS 2018/19 SB14Z Day case (60min IV infusion)

Abbreviations: NICE: National Institute for Health and Care Excellence; SE: standard error; TA: technology appraisal.
Source: TA520;[86] TA557;[47] TA584;[50] NHS Reference Costs 2018–19;[88] PSSRU 2019.[89]

Table 66: Drug administration costs for selpercatinib and comparators in the second line setting

Treatment	Mean cost, £	SE, £	Lower bound, £	Upper bound, £	Source
Selpercatinib	9.20	0.92	7.40	11.00	NICE TA520; PSSRU 2019 Table 9 Band 6 hourly wage (12 min pharmacy time)
Pembrolizumab	185.00	18.50	148.74	221.26	NICE TA520; NHS 2018/19 SB12Z Outpatient (30 min IV infusion)
Nivolumab	185.00	18.50	148.74	221.26	NICE TA520; NHS 2018/19 SB12Z

					Outpatient (60 min IV infusion)
Nintedanib + docetaxel	194.20	19.42	156.14	232.26	NICE TA520; PSSRU 2019 Table 9 Band 6 hourly wage (12 min pharmacy time); NICE TA520; NHS 2018/19 SB12Z Outpatient (60 min IV infusion)
Atezolizumab	185.00	18.50	148.74	221.26	NICE TA520; NHS 2018/19 SB12Z Outpatient (60 min IV infusion)

Abbreviations: IV: intravenous; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.
Source: TA520;[86] NHS Reference Costs 2018–19;[88] PSSRU 2019.[89]

Subsequent treatments

The pattern of subsequent treatments for NSCLC following first line therapy was based on the type of treatment received at first line, as categorised as selpercatinib or immunotherapy. The proportion of patients expected to receive each therapy was based on the most recent relevant NICE appraisals: TA584, TA531, TA520, TA484 and TA347. For immunotherapies, estimates in TA584 for atezolizumab combinations are assumed to apply to all immunotherapies (single-agent and combination comparators). For selpercatinib, estimates are based on subsequent treatments applied to other immunotherapies.

The pattern of subsequent treatments for NSCLC following second line therapy was based on the type of treatment originally received, as categorised as selpercatinib, immunotherapy or chemotherapy, as informed by the NICE appraisals TA520 and TA347. The pattern of subsequent treatments for selpercatinib is assumed to be similar to immunotherapies.

The subsequent treatment costs consider the time on treatment for subsequent therapy, associated administration costs, and the fraction of the patients receiving each post-progression therapy. The cost estimates for the percentage of patients expected to receive each subsequent therapy after first line or treatment are presented in Table 67, whilst the cost estimates for the percentage of patients expected to receive each subsequent therapy after second line are presented in Table 68.

Table 67: Subsequent therapy cost estimates following first line treatment

Therapy	Mean cost, £	SE, £	Lower bound, £	Upper bound, £	Patients treated with, proportion	
					Selpercatinib	Immunotherapy
Docetaxel	270.52	13.80	217.50	324.54	56.0%	100.0%
Nivolumab	32,046.49	1,635.05	25,765.38	38,328.60	0.0%	0.0%
Pembrolizumab	27,798.81	1,418.33	22,350.24	33,247.37	0.0%	0.0%
Atezolizumab	82,243.47	4,196.17	66,123.75	98,363.19	0.0%	0.0%
Carboplatin	73.84	3.77	59.37	88.32	44.0%	0.0%

Abbreviations: SE: standard error**.**
Source: TA584;[50] TA531,[49] and TA484.[84]

Table 68: Subsequent therapy distribution estimates following second line treatment

Therapy	Mean cost, £	SE, £	Lower bound, £	Upper bound, £	Patients treated with, proportion		
					Selpercatinib	Immunotherapy	Chemotherapy
Docetaxel	765.09	39.04	688.58	841.59	14.9%	14.9%	0.0%
Carboplatin	1,215.60	62.02	1,094.04	1,337.17	8.7%	8.7%	25.0%
Gemcitabine	2,925.86	149.28	2,633.28	3,218.45	7.7%	7.7%	7.7%
Erlotinib	4,136.30	211.04	3,722.67	4,549.93	5.5%	5.5%	5.5%
Pemetrexed	8,976.06	457.97	8,078.45	9,873.66	4.9%	4.9%	0.0%
Vinorelbine	3,946.53	201.36	3,551.88	4,341.19	5.1%	5.1%	5.1%
Radiotherapy	7,717.50	393.76	6,945.75	8,489.25	55.0%	55.0%	56.6%

Abbreviations: SE: standard error
Source: TA520,[86] TA347.[95]

B.3.5.2 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 appraisals and subsequently validated by clinicians. Resource use per health state are reported in Table 69 and Table 70 for the first and second line cost-effectiveness analyses, respectively. In the first line setting, the per cycle cost for the PFS health state was £72.46, whilst the per cycle costs for PD was £111,82. In the second line setting, the per cycle cost for the PD health state was £141.03, whilst the per cycle costs for PD was £128.59.

Table 69: Resource use per 30-day period in first line NSCLC, by health state

Resource	Progression free	Progressed disease	Unit cost, £	Total PF, £	SE PF, £	Total PD, £	SE PD, £
Outpatient visit	0.79	0.65	143.00	112.97	11.30	92.95	9.30
Chest radiography	0.56	0.53	31.00	17.36	1.74	16.43	1.64
CT scan (chest)	0.05	0.02	97.00	4.85	0.49	1.94	0.19
CT scan (other)	0.03	0.03	97.00	2.91	0.29	2.91	0.29
ECG	0.09	0.07	49.00	4.41	0.44	3.43	0.34
Community nurse visit	0.71	0.71	24.55	17.43	1.74	17.43	1.74
Clinical nurse specialist	0.99	0.99	110.00	108.90	10.89	108.90	10.89
GP surgery	0.99	0	42.12	41.70	4.17	0.00	0.00
GP home visit	0	2.14	61.92	0.00	0.00	132.51	13.25
Therapist visit	0	2.14	48.00	0.00	0.00	102.72	10.27

Abbreviations: CT: Computerised tomography; ECG: electroocardiogram; GP: general practitioner; NSCLC: non–small cell lung cancer.
Source: TA621,[83] NHS Reference Costs 2018–19,[88] PSSRU 2019.[89]

Table 70: Resource use per 3-week period in second line NSCLC, by health state

Resource	Progression-Free	Progressed disease	Unit cost, £	Total PF, £	SE PF, £	Total PD, £	SE PD, £
GP surgery visit	0.63	1	42.12	26.54	2.65	42.12	4.21
GP home visit	0	0.25	61.92	0.00	0.00	15.48	1.55
Oncologist visit	0.80	0.46	198.00	158.40	15.84	91.08	9.11
Full blood test	1	1	3.00	3.00	0.30	3.00	0.30
Liver function test	1	0.46	1.00	1.00	0.10	0.46	0.05
Renal function test (with electrolytes)	1	0.46	1.00	1.00	0.10	0.46	0.05
CT scan (thorax or abdominal)	0.28	0.28	97.00	27.16	2.72	27.16	2.72
Palliative care days	2	2	103.00	206.00	20.60	206.00	20.60

Abbreviations: CT: Computerised tomography; GP: general practitioner; NSCLC: non–small cell lung cancer.
Source: TA520;[86] NHS Reference Costs 2018–19;[88] PSSRU 2019.[89]

B.3.5.3 Adverse reaction unit costs and resource use

Mean cost per adverse event applied in the first and second line cost-effectiveness analyses are reported in Table 71. Adverse event costs were applied in the model according to the incidences presented in Section B.3.4.4.

Table 71: Costs per adverse event applied in the first and second line cost-effectiveness model

Adverse event	Mean cost, £	SE	Lower bound, £	Upper bound, £	Source
Diarrhoea	2,601.49	260.15	2,091.60	3,111.38	NHS Reference costs 2018/19 (FD10A-M); TA621
Hypertension	1,134.52	113.45	912.16	1,356.89	NHS Reference costs 2018/19 (EB04Z); TA516
ECG QT prolonged	1,027.53	102.75	826.14	1,228.93	NHS Reference costs 2018/19 (EB07E); TA516
Fatigue	3,446.26	344.63	2,770.80	4,121.73	NHS Reference costs 2018/19 (SA01G-SA01K); TA621
Decreased appetite	6,832.96	683.30	5,493.70	8,172.22	NHS Reference costs 2018/19 (FD04A-B); TA516
Asthenia	3,446.26	344.63	2,770.80	4,121.73	NHS Reference costs 2018/19 (SA01G-SA01K); TA621
Vomiting	2,601.49	260.15	2,091.60	3,111.38	NHS Reference costs 2018/19

					(FD10A-M); Assumption
Dyspnoea	0.00	0.00	0.00	0.00	NHS Reference costs 2018/19; TA484
Alanine aminotransferase increased	2,621.08	262.11	2,107.35	3,134.81	NHS Reference costs 2018/19 (GC17A–K); TA621
Aspartate aminotransferase increased	2,621.08	262.11	2,107.35	3,134.81	NHS Reference costs 2018/19 (GC17A–K); TA621
Hyponatraemia	0.00	0.00	0.00	0.00	Assumption
Lymphopenia	5,100.10	510.01	4,100.48	6,099.72	NHS Reference costs 2018/19 (SA17G-H); Assumption
Pneumonia	2,472.08	247.21	1,987.55	2,956.61	NHS Reference costs 2018/19 (DZ11T); Assumption
Thrombocytopenia	3,091.86	309.19	2,485.85	3,697.86	NHS Reference costs 2018/19 (SA12G-K, weighted); Assumption
Neutropenia	2,617.33	261.73	2,104.33	3,130.33	NHS Reference costs 2018/19 (SA35A-E, weighted); Assumption
Anaemia	1,412.32	141.23	1,135.51	1,689.14	NHS Reference costs 2018/19 (SA04H); TA520
Pleural effusion	2,905.14	290.51	2,335.73	3,474.55	NHS Reference costs

					2018/19 (DZ16L-N, weighted); Assumption
Febrile neutropenia	5,687.85	568.79	4,573.03	6,802.67	TA484
Pneumonitis	3,908.20	390.82	3,142.20	4,674.21	NHS Reference costs 2018/19 (DZ11Q-N, weighted); Assumption
Nausea	2,601.49	260.15	2,091.60	3,111.38	NHS Reference costs 2018/19 (FD10A-M, weighted); Assumption
Hepatitis Lab abnormalities	0.00	0.00	0.00	0.00	Assumption
Sepsis	4,492.56	449.26	3,612.02	5,373.11	NHS Reference costs 2018/19 (WJ06D-F, weighted); Assumption
Acute kidney injury	1,456.00	145.60	1,170.62	1,741.38	Assumption
Chronic obstructive pulmonary disease	2,814.54	281.45	2,262.89	3,366.19	NHS Reference costs 2018/19 (DZ65C-E, weighted); Assumption
Urinary tract infection	3,907.27	390.73	3,141.44	4,673.09	NHS Reference costs 2018/19 (LA04H-M, weighted); Assumption
Peripheral neuropathy	1,181.44	118.14	949.88	1,413.01	Song et al., 2019
Decreased platelet count	3,091.86	309.19	2,485.85	3,697.86	NHS Reference costs 2018/19 (SA12G-K, weighted); Assumption

Decreased neutrophil count	2,617.33	261.73	2,104.33	3,130.33	NHS Reference costs 2018/19 (SA35A-E, weighted); Assumption
Severe skin reaction	2,832.23	283.22	2,277.11	3,387.35	NHS Reference costs 2018/19 (JD07A-K, weighted); TA621
Proteinuria	0.00	0.00	0.00	0.00	Assumption

Abbreviations: ECG: echocardiogram; NHS: National Health Service; SE: standard error; TA: technology appraisal.
Source: NHS Reference costs 2018/19;[88] TA621;[83] TA516;[111] TA484;[84] TA520.[86]

B.3.5.4 Miscellaneous unit costs and resource use

A one-off end of life cost of £4,248.20 (first line; Table 72) and £3,630.88 (second line; Table 73) was also included based on costs included in TA621 and TA520, respectively, which considered hospital admission and excess bed days, Macmillan nurse home visits and hospice care stays.

Table 72. End of life costs in the second line setting

	Mean	Patients, proportion	Unit costs, £	Total cost, £	SE, £
Hospital admission + excess bed days	1.00 0.92	55.8% 55.8%	3,282.23 304.00	1,831.49 156.06	183.15 15.61
Macmillan nurse home visits	1.00	27.3%	5,740.95	1,567.28	156.73
Hospice care stay	1.00	16.9%	4,102.79	693.37	69.34

Source: TA621[83]

Table 73. End of life costs in the second line setting

	Mean	Patients, proportion	Unit costs, £	Total cost, £	SE, £
Hospital admission + excess bed days	1.00 0.84	55.8% 55.8%	4,027.00 725.00	2,247.07 339.82	224.71 33.98
Macmillan nurse home visits	50.00	27.3%	14.16	193.29	19.33
Hospice care stay	1.00	16.9%	5,033.75	850.70	85.07

Source: TA520[86]

As described in Section B.1.3.2, due to the imminent establishment of Genomic Hubs, whereby testing for RET and other genetic mutations of tumour samples will become routine, no costs for genetic testing have been included in the analysis, as it has been assumed they would be absorbed by the health care system.

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

B.3.6.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis for the first and second line settings is presented in Table 74.

Table 74: Summary of variables applied in the base case analysis

Variable	First line *RET*-fusion positive NSCLC	Second line *RET*-fusion positive NSCLC	Reference to section in submission
Model settings			
Discount rate (costs)	3.5%		Section B.3.2.2
Discount rate (benefits)	3.5%		
Time horizon	Lifetime: 25 years		
Patient characteristics			
Starting age (SE)	[redacted]	[redacted]	Section B.3.3.1
Percent female (SE)	[redacted]	[redacted]	
Mean weight (SE)	[redacted]	[redacted]	
Mean BSA (SE)	1.81 (0.1) m^2	1.81 (0.1) m^2	
Clinical inputs			
OS (selpercatinib)	Equal PPS (exponential)	Unstratified exponential	Section B.3.3.2
PFS (selpercatinib)	Stratifed lognormal	Stratified gamma	
OS (reference arm and comparators)	Equal PPS (exponential)	Unstratified Weibull	
PFS (reference arm and comparators)	Unstratified Gompertz	Unstratified Weibull	
NMA HRs (comparators)	*Various*	*Various*	Section B.2.8
TTD (selpercatinib)	Equal to PFS	Equal to PFS	Section B.3.3.3
Adverse events, incidence	*Various*	*Various*	Section B.3.3.4
Utility inputs			
Utility for PFS	0.794	0.713	Section B.3.4
Utility for PD	0.678	0.688	
Drug acqusition costs			
Selpercatinib price: 60 x 80 mg tablets	[redacted]		Section B.3.5.1
Selpercatinib price: 60 x 80 mg tablets	[redacted]		
Pembrolizumab: 4 ml (25 mg/ml vials)	£2,630.00		
Atezolizumab 20 ml (60 mg/ml vials)	£3,807.69		
Nivolumab: 4 ml (10 mg/ml vials)	NA	£439.00	
Nintedanib	NA	£2,151.10	
Docetaxel 8 ml (160 mg/ml vials)	NA	£16.80	

Include drug wastage	Yes	Yes	Section B.3.5.1
Cost per treatment cycle: selpercatinib	*Various*	*Various*	Section B.3.5.1
Cost per treatment cycle: comparators	*Various*	*Various*	
Dose intensity (all interventions) (SE)	[redacted] (1.9%)	[redacted] (1.9%)	
Drug administration costs (SE)			Section B.3.5.1
Selpercatinib	£9.20 (0.92)	£9.20 (0.92)	
Pembrolizumab	185.00 (£18.50)	185.00 (£18.50)	
Pembrolizumab combination	£502.73 (£50.27)	NA	
Atezolizumab combination	£385.28 (£38.53)	NA	
Nintedanib plus docetaxel	NA	194.20 (£19.42)	
Atezolizumab	NA	185.00 (£18.50)	
Nivolumab	NA	185.00 (£18.50)	
Monitoring costs per cycle (SE)	£64.67 (£6.47)	£64.67 (£6.47)	Section B.3.5.1
Subsequent therapy			
Selpercatinib (SE)	£201.22 (£20.12)	£5,560.15 (£556.01)	Section B.3.5.1
Immunotherapy (SE)	£301.30 (£30.13)	£5,560.15 (£556.01)	
Chemotherapy (SE)	£37,029.83 (3,702.98)	£5,330.72 (£533.07)	
Health state costs			
Health state costs per cycle: PFS (SE)	£72.46 (37.25)	£141.03 (£14.10)	Section B.3.5.2
Health state costs per cycle: PD (SE)	£111.82 (£11.18)	£128.59 (£12.86)	
Other costs			
Adverse event costs	*Various*	*Various*	Section B.3.5.3
End of life costs (SE)	£4,248.20 (£424.82)	£3,630.88 (£363.09)	Section B.3.5.4

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.3.6.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 75.

Table 75: Modelling assumptions for first line *RET* fusion-positive NSCLC

Parameter (setting)	Assumption	Justification	Addressed in scenario analysis
PFS and OS comparator arm extrapolations (first and second line)	The parametric survival function selected for the reference arm in each setting was	The parametric survival curve selected for the reference arm for OS and PFS in each setting was limited to	Alternative parametric survival functions for PFS and OS in both settings are explored in scenario analyses.

	deemed appropriate to represent comparators relevant to the decision problem.	proportional hazards functions. 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.	
Proportional hazards assumption (first and second line)	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.
Over-estimation of reference arm and comparator extrapolations for PFS and OS (first and second line)	Application of the time acceleration factor and TMLE resulted in overly-optimistic PFS and OS predictions for reference arms and comparators in both settings. Base case parametric function selections were informed by expert clinical opinions in order to generate clinically plausible curves.	Emphasis was placed on the selection of clinically plausible extrapolations for PFS and OS in both settings.	Alternative parametric survival functions for PFS and OS in both settings are explored in scenario analyses.
Equal PPS (first line)	Survival following progression after first line treatment is assumed to be equal between selpercatinib and comparators.	This conservative assumption was made due to the immature OS data currently available for first line patients from LIBRETTO-001.	Scenario analyses are conducted whereby OS for selpercatinib is based on PFS as a surrogate and where extrapolation of trial data is explored.
Atezolizumab PFS HR (second line)	In the absence of PFS data for atezolizumab in the second line setting, the PFS HR for nivolumab from the second line NMA was utilised to inform the atezolizumab PFS HR in the model.	Data for OS from clinical trials indicate that atezolizumab is similar in efficacy to nivolumab (OS HR for nivolumab [all patients] versus atezolizumab = 1.06 [95% CrIs: 0.48–2.36]).[58]	N/A
Selpercatinib data informing PD-L1	In the absence of subgroup data by	This assumption was necessary in order to	N/A

subgroups (first and second line)	PD-L1 status from LIBRETTO-001, data from the full population (either SAS1 [first line] or the IAS [second line] were used to inform the PD-L1 patient group analyses.	make comparisions between selpercatinib and comparators specified in the final scope indicated in specific PD-L1 subgroups.	
Drug wastage (first and second line)	In the base case, wastage is assumed for IV treatments but not for oral drugs.	It is possible for vials utilised for IV infusions to be discarded, whilst it is not routine practice to split tablets.	A scenario analysis is conducted whereby the minimum price per mg is applied to accurately capture the RDI in the LIBRETTO-001 trial. Vial sharing is assumed in this scenario.
Utility values (first and second line)	Utility values based on prior NICE NSCLC appraisals are used to inform the base case HSUVs, as no *RET* fusion-specific utility data are available.	Clinical opinion was that the HRQoL of patients with NSCLC more broadly would be representative of NSCLC driven by a *RET* fusion genetic alteration.	Alternative HSUVs are explored in scenario analyses.

Abbreviations: CrI: credible interval; HR: hazard ratio; HRQoL: health-related quality of life; HSUVs: health state utility values; IV: intravenous; NMA: network meta-analysis; NSCLC: non-small cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression free survival; PPS: post progression survival; TMLE: targeted minimum loss-based estimation

B.3.7 *Base-case results*

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

A summary of the base case analysis for *RET* fusion-positive NSCLC in the first and second line settings are presented below. 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.

First line setting

The base case cost-effectiveness results for selpercatinib versus the relevant comparators for use in all patients, the PD-L1<50% subgroup and the PD-L1≥50% subgroup in the first line setting are presented in Table 76, Table 76 and Table 78, respectively. The results illustrate that in all patient groups versus all comparators, selpercatinib is associated with greater QALYs and LYG, reflecting the high levels of efficacy of selpercatinib in the first line *RET* fusion-positive NSCLC population. The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] for pembrolizumab combination, [redacted] for atezolizumab combination and [redacted] for pembrolizumab monotherapy. This resulted in an ICER of [redacted], [redacted] and [redacted] per QALY gained, respectively. It should be noted that these results are presented at list price for selpercatinib and comparators, [redacted].

Table 76: Base-case results first line *RET* fusion-positive NSCLC (all patients): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 77: Base-case results first line *RET* fusion-positive NSCLC (PD-L1<50%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 78: Base-case results first line *RET* fusion-positive NSCLC (PD-L1≥50%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Second line *RET* fusion-positive NSCLC

The base case cost-effectiveness results for selpercatinib versus the relevant comparators for use in all patients and the PD-L1≥1% subgroup in the second line setting are presented in Table 79 and Table 80, respectively. The results illustrate that in all patient groups versus all comparators, selpercatinib is associated with greater QALYs and LYG, reflecting the high levels of efficacy of selpercatinib in the second line *RET* fusion-positive NSCLC population. The total QALYs for patients receiving selpercatinib are estimated to be [redacted] compared with [redacted] and [redacted] for patients treated with atezolizumab and nintedanib + docetaxel, respectively, and [redacted] and [redacted] for pembrolizumab and nivolumab, respectively, in the PD-L1≥1% subgroup. This resulted in pairwise ICERs for selpercatinib of £[redacted], [redacted], [redacted] and [redacted] per QALY gained versus nintedanib + docetaxel, atezolizumab, nivolumab and pembrolizumab, respectively. However, it should be noted that these results are presented at list price for selpercatinib and comparators, [redacted].

Disaggregated cost-effectiveness results for the second line setting are presented in Appendix J.

Table 79: Base-case results second line *RET* fusion-positive NSCLC (all patients): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

Table 80: Base-case results second line *RET* fusion-positive NSCLC (PD-L1≥1%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

End of life criteria

As discussed in Section B.2.11, there is evidence to support selpercatinib meeting the end of life criteria for the comparison in the second line setting to nintedanib plus docetaxel. The full disaggregated cost-effectiveness results are presented in Appendix J, however, for ease of assessment, the disaggregated results for the pairwise cost-effectiveness analysis between selpercatinib and nintedanib plus docetaxel are also presented in Table 81Table 82. The results illustrate that selpercatinib is associated with an increase in survival of [redacted] compared to nintedanib plus docetaxel. Nintedanib plus docetaxel itself is associated with an estimated survival, which is considered to be an optimistic, of [redacted].

Table 81: Second line base case clinical outcomes: PFS and OS

Intervention/comparator	Median PFS (months)	Median OS (months)
Selpercatinib	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]

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

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analyses (PSA) were run with 1,000 iterations for each patient group of interest, 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.
The distributions of input parameters varied in the PSA are presented in Table 82. Input parameters that were varied within their standard errors are presented in Section B.3.6.1.

Table 82. Input parameter distributions in the PSA

Input parameter	Distribution used in the PSA
Starting age	Normal
Percentage female	Beta
Mean weight	Normal
Mean BSA	Normal
PFS selpercatinib parametric function (first and second line)	Variance covariance matrix (correlated normal)
PFS reference arm function (first and second line)	Variance covariance matrix (correlated normal)
OS selpercatinib parametric function (first and second line)	Variance covariance matrix (correlated normal)
OS reference arm function (first and second line)	Variance covariance matrix (correlated normal)
TTD for selpercatinib and reference arms parametric function (utilises PFS curves)	Variance covariance matrix (correlated normal)
Mortality ratio	Normal
Utility: PFS	Beta
Utility: PD	Beta
Per cycle treatment costs	
Selpercatinib	Fixed
Pembrolizumab combination	Varies with BSA
Atezolizumab combination	Varies with weight and BSA
Pembrolizumab (first line)	Fixed
Nivolumab	Fixed
Atezolizumab	Fixed
Nintedanib plus docetaxel	Varies with BSA
Pembrolizumab (second line)	Fixed
Dose intensity (selpercatinib and comparators)	Beta
Drug administration costs	Gamma
Monitoring cost	Gamma
Subsequent therapy	Varies with dose intensity, weight, BSA and administration costs

Health state costs	Gamma
Terminal care	Gamma

Abbreviations: BSA: body surface area; OS: overall survival; PFS: progression free survival; PD: progressed disease; TTD: time to discontinuation

The probabilistic base case results for the first line setting are presented in Table 83**First line setting**

Table 83, Table 84 and Table 85. The probabilistic base case results for the second line setting are presented in Table 86 and Table 87.

First line setting

Table 83: Probabilistic base-case results first line *RET* fusion-positive NSCLC (all patients): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 84: Probabilistic base-case results first line *RET* fusion-positive NSCLC (PD-L1<50%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 85: Probabilistic base-case results first line *RET* fusion-positive NSCLC (PD-L1≥50%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Second line setting

Table 86: Probabilistic base-case results second line *RET* fusion-positive NSCLC (all patients): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER (£/QALY)[a]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-

Footnotes: [a]Pairwise: selpercatinib vs comparator
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PSA: probabilistic sensitivity analyses; QALYs: quality-adjusted life years

Table 87: Probabilistic base-case results second line *RET* fusion-positive NSCLC (PD-L1≥1): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs[a]	Incremental LYG[a]	Incremental QALYs[a]	ICER incremental (£/QALY)[a]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	-	-	-	-

Footnotes: [a]Pairwise: selpercatinib vs comparator
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus pembrolizumab combination, atezolizumab combination and pembrolizumab monotherapy in the first line setting are presented in Figure 47, Figure 48 and Figure 49, respectively.

Figure 47. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs pembrolizumab combination in the first line setting

[redacted]

[redacted]

Abbreviations: QALY: quality-adjusted life year.

Figure 48. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs atezolizumab combination (PD-L1<50%) in the first line setting

[redacted]

Abbreviations: QALY: quality-adjusted life year.

Figure 49. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs pembrolizumab (PD-L1≥50%) in the first line setting

[redacted]

[redacted]

Abbreviations: QALY: quality-adjusted life year.

Second line setting

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus nintedanib plus docetaxel, atezolizumab, nivolumab and pembrolizumab in the second line setting are presented in Figure 50 and Figure 51, respectively.

Figure 50. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs nintedanib + docetaxel and selpercatinib vs atezolizumab in the second line setting

[redacted]

[redacted]

Abbreviations: QALY: quality-adjusted life year.

Figure 51. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs nivolumab and selpercatinib vs pembrolizumab (PD-L1≥1%) in the second line setting

[redacted]

B.3.8.2 Deterministic sensitivity analysis

First line setting

The tornado diagrams for selpercatinib versus pembrolizumab combination, atezolizumab combination and pembrolizumab monotherapy in the first line setting are presented in Figure 52, Figure 53 and Figure 54, respectively. The top 25 most influential parameters on the base case are presented in each case.

Figure 52. DSA tornado diagram for selpercatinib vs pembrolizumab combination in the first line setting

[redacted]

Figure 53. DSA tornado diagram for selpercatinib vs atezolizumab combination (PD-L1<50%) in the first line setting

[redacted]

Figure 54. DSA tornado diagram for selpercatinib vs pembrolizumab (PD-L1≥50%) in the first line setting

[redacted]

Second line setting

The tornado diagrams for selpercatinib versus nintedanib plus docetaxel, atezolizumab, nivolumab and and pembrolizumab in the second line setting are presented in Figure 55, Figure 56, Figure 57 and Figure 58, respectively. The top 25 most influential parameters on the base case are presented in each case.

Figure 55. DSA tornado diagram for selpercatinib vs nintedanib + docetaxel in the second line setting

[redacted]

Figure 56. DSA tornado diagram for selpercatinib vs atezolizumab in the second line setting

[redacted]

Figure 57. DSA tornado diagram for selpercatinib vs nivolumab (PD-L1≥1%) in the second line setting

[redacted]

Figure 58. DSA tornado diagram for selpercatinib vs pembrolizumab (PD-L1≥1%) in the second line setting

[redacted]

B.3.8.3 Scenario analysis

A summary of the scenario analysis results for selpercatinib versus relevant comparators in the first line population are presented in Table 88. It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and the reference arm. With regards to scenarios for OS, these scenarios assume that the 'equal PPS' assumption made in the base case does not apply.

Table 88: Scenario analysis results for selpercatinib versus relevant comparators in the first line setting

Scenario		All patients; vs pembrolizumab combination		PD-L1<50%; vs atezolizumab combination		PD-L1≥50%; vs pembrolizumab	
		ICER	% ICER change	ICER	% ICER change	ICER	% ICER change
1	Discount rate 1.5% benefits	[redacted]	-5.27%	[redacted]	-5.04%	[redacted]	-5.09%
2	Discount rate 6%, costs and benefits	[redacted]	6.50%	[redacted]	6.19%	[redacted]	6.33%
3	Undiscounted health outcomes and costs	[redacted]	-9.25%	[redacted]	-8.85%	[redacted]	-8.93%
4	Utilities, TA310 PF: 0.784 PD: 0.517	[redacted]	-0.79%	[redacted]	-0.76%	[redacted]	-0.74%
5	Utilities, TA536 PF: 0.814 PD: 0.725	[redacted]	-2.07%	[redacted]	-2.08%	[redacted]	-2.08%
6	Utilities, Chouiad et al. PF: 0.71 PD: 0.67	[redacted]	12.89%	[redacted]	12.90%	[redacted]	12.90%
7	Minimum price per mg	[redacted]	-25.33%	[redacted]	-21.02%	[redacted]	-6.35%
8	Curve choice: OS – Exponential	[redacted]	-26.74%	[redacted]	-59.14%	[redacted]	-43.39%
9	Curve choice: OS – Weibull	[redacted]	270.25%	[redacted]	111.38%	[redacted]	189.98%
10	Curve choice: OS – Gompertz	[redacted]	2136.14%	[redacted]	1000.79%	[redacted]	1418.84%
11	Curve choice: OS – spline knot 1	[redacted]	66.95%	[redacted]	6.25%	[redacted]	40.10%
12	Curve choice: OS – spline knot 2	[redacted]	148.38%	[redacted]	47.61%	[redacted]	97.60%

13	Curve choice: PFS – Exponential	[redacted]	-12.48%	[redacted]	-9.83%	[redacted]	-11.54%
14	Curve choice: PFS – Weibull	[redacted]	-18.77%	[redacted]	-15.95%	[redacted]	-11.68%
15	Curve choice: PFS – Gompertz	[redacted]	-13.58%	[redacted]	-10.91%	[redacted]	-7.25%
16	Curve choice: PFS – spline knot 1	[redacted]	-0.88%	[redacted]	1.35%	[redacted]	-8.39%
17	Curve choice: PFS – spline knot 2	[redacted]	-14.74%	[redacted]	-11.97%	[redacted]	-12.12%
18	Curve choice: PFS – stratified Weibull	[redacted]	-	[redacted]	-	[redacted]	146.38%
19	Curve choice: PFS – Stratified Gompertz	[redacted]	-93.83%	[redacted]	-	[redacted]	-
20	Curve choice: PFS – stratified gamma (selpercatinib arm)	[redacted]	143.11%	[redacted]	63.92%	[redacted]	28.33%
21	PFS surrogate	[redacted]	-62.41%	[redacted]	-58.21%	[redacted]	-56.68%

*indicates [redacted] dominated

Abbreviations: ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; OS: overall survival.

A summary of the scenario analysis results for selpercatinib versus relevant comparators in the second line population are presented in Table 89.
It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and the reference arm.

Table 89: Scenario analysis results for selpercatinib versus relevant comparators in the second line setting

Scenario		All patients				PD-L1≥1%			
		ICER vs atezolizumab	% ICER change	ICER vs nintedanib+ docetaxel	% ICER change	ICER vs pembrolizumab	% ICER change	ICER vs nivolumab	% ICER change
1	Discount rate 1.5%, benefits	[redacted]	-17.11%	[redacted]	-13.20%	[redacted]	-18.00%	[redacted]	-16.85%
2	Discount rate 6%, costs and benefits	[redacted]	19.60%	[redacted]	12.69%	[redacted]	20.64%	[redacted]	19.20%
3	Undiscounted health outcomes and costs	[redacted]	-23.91%	[redacted]	-16.93%	[redacted]	-24.80%	[redacted]	-23.54%
4	Utilities, TA416 PF: 0.853 PD: 0.659	[redacted]	23.05%	[redacted]	-1.48%	[redacted]	-9.29%	[redacted]	-3.93%
5	Utilities, TA310,TA252 PF: 0.672 PD: 0.6532-0.1798 (0.473)	[redacted]	23.64%	[redacted]	33.57%	[redacted]	18.86%	[redacted]	28.90%
6	Utilities, TA416 PF: 0.687 PD: 0.64	[redacted]	5.71%	[redacted]	6.58%	[redacted]	5.24%	[redacted]	6.19%

7	Minimum price per mg	[redacted]	-19.87%	[redacted]	-12.88%	[redacted]	-3.49%	[redacted]	-17.42%
8	Curve choice: OS – Exponential	[redacted]	380.40%	[redacted]	12.67%	[redacted]	-	[redacted]	246.01%
9	Curve choice: OS – Weibull	[redacted]	729.36%	[redacted]	43.35%	[redacted]	-	[redacted]	426.39%
10	Curve choice: OS – Gompertz	[redacted]	5529.63%	[redacted]	23.09%	[redacted]	-	[redacted]	284.70%
11	Curve choice: OS – spline knot 1	[redacted]	256.30%	[redacted]	-2.40%	[redacted]	-	[redacted]	173.08%
12	Curve choice: OS – spline knot 2	[redacted]	227.75%	[redacted]	-8.99%	[redacted]	31229.11%	[redacted]	154.17%
13	Curve choice: OS – stratified Weibull	[redacted]	-	[redacted]	765.19%	[redacted]	-	[redacted]	-
14	Curve choice: OS – stratified Gompertz	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-
15	Curve choice OS – Gompertz (selpercatinib arm only)	[redacted]	94.15%	[redacted]	8.30%	[redacted]	67.74%	[redacted]	41.04%
16	Curve choice: PFS – Exponential	[redacted]	73.10%	[redacted]	59.70%	[redacted]	82.08%	[redacted]	73.60%

17	Curve choice: PFS – Weibull	[redacted]	48.68%	[redacted]	37.65%	[redacted]	51.36%	[redacted]	49.17%
18	Curve choice: PFS – Gompertz	[redacted]	203.58%	[redacted]	175.43%	[redacted]	241.30%	[redacted]	205.88%
19	Curve choice: PFS – spline knot 1	[redacted]	246.01%	[redacted]	216.58%	[redacted]	301.47%	[redacted]	250.01%
20	Curve choice: PFS – spline knot 2	[redacted]	110.16%	[redacted]	91.92%	[redacted]	126.44%	[redacted]	110.87%
21	Curve choice: PFS – stratified Weibull	[redacted]	-13.75%	[redacted]	-8.84%	[redacted]	-11.81%	[redacted]	-14.05%
22	Curve choice: PFS – Stratified Gompertz	[redacted]	-	[redacted]	-30.92%	[redacted]	-30.80%	[redacted]	-93.68%
23	Equal PPS	[redacted]	121.88%	[redacted]	321.41%	[redacted]	76.36%	[redacted]	202.04%

*indicates [redacted] dominated

Abbreviations: ICER: incremental cost-effectiveness ratio;OS: overall survival; PD: progressed disease; PD-L1: programmed death-ligand 1; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival.

B.3.8.4 Summary of sensitivity analyses results

The results of the probabilistic base case were closely reflective of the deterministic analysis, demonstrating that the model is robust to variation in input parameters. This was mirrored in the results of the deterministic sensitivity analyses, where 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. In the first line setting, the greatest drivers of the ICER were consistently HSUVs values and administration and monitoring costs, whilst in the second line setting HSUVs had the greatest influence on the ICER.

With regards to structural variation, the results of the scenario analyses in the first line setting demonstrated that the ICER is most sensitive to variations in the parametric survival functions used to extrapolate OS and PFS. As discussed in Section B.3.3.2, significant importance was placed on the clinical plausibility of the extrapolations, with feedback sought from an expert oncologist practicing in the NHS in order to ensure the selection of the most appropriate functions. The scenarios with the greatest influence on the ICER apply parametric functions that were deemed by the expert clinician to be clinically implausible to both the selpercatinib and reference arms, leading to use of the 'equal PPS' scenario instead, and it is therefore considered that these ICERs are highly unlikely to be valid.

The results of the scenario analyses in the second line setting similarly demonstrate that the ICER is most sensitive to variations in the parametric survival functions used to extrapolate OS and PFS. As per the first line setting, selection of parametric survival functions was closely guided by expert clinical input in order to maximise clinical plausibility. As such, the extrapolations selected for the base case are considered to possess the greatest face validity of all extrapolation choices.

B.3.9 *Subgroup analysis*

The results for patient subgroups of interest are presented in the sections above.

B.3.10 *Validation*

Face validity

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC. Of note, and as discussed in Sections B.3.3.2 and B.3.8.4, in light of the currently immature survival data available from the LIBRETTO-001 trial, a thorough clinical validation process was conducted in order to inform survival analysis for the PFS and 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. In addition, the model was validated by an independent health economist.

Cross validity

Comparison of results with other models analysing the same problem was to be performed where suitable models were available. Because no economic evaluations have been performed in RET-altered NSCLC, cross validation was not possible.

External validity

Validation of the clinical outcomes predicted by the model for the second line setting was conducted against published outcomes for selpercatinib and comparators, as presented in Table 90. It can be observed from this comparison that the median PFS prediction for selpercatinib closely aligns with the trial ([redacted] vs [redacted] months). However, the results suggest that the model predicts overly optimistic estimates for comparators, with all model estimates greater (substantially in some cases) than trial outcomes. As discussed in Section B.3.3.2, feedback from the expert clinician was that application of the time acceleration factor to adjust for *RET* fusion status, in addition to use of the TMLE adjustment for other prognostic factors, has resulted in overestimates for PFS and OS for the reference arm, and thus the comparators for which HRs from the NMAs are applied. The clinician noted that the extent of this was greater for the second line than the first line. The impact of this on the analysis is that the cost-effectiveness results for selpercatinib are likely to be highly conservative, as the true difference in treatment effect between selpercatinib and comparators has not been fully realised.

This is further supported by a study conducted by Offin et al., who found that the median PFS for *RET*-rearranged NSCLC patients treated with immunotherapies (the median line of therapy at which treatment was administered was 2) was lower than for patients treated with chemotherapy, at just 3.4 months (95% CI: 2.1 to 5.6 months). The authors of the study suggest there is a possibility that *RET*-altered tumours may be 'biologically cold', whereby they are less responsive to immunotherapy relative to other cancers. This evidence further suggests that this analysis is likely overestimates survival in immunotherapy comparators in this patient population.

Table 90: External validation of second line model outcomes against published PFS and OS estimates (months)

	Trial mPFS	Predicted mPFS	Trial mOS	Predicted mOS
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib+docetaxel	4.2 (TA347)	[redacted]	12.6 (TA347)	[redacted]
Atezolizumab	-	[redacted]	13.8 (OAK study)	[redacted]
PD-L1≥1% subgroup				
Nivolumab	2.3 (Checkmate 057 – ITT)	[redacted]	12.2 (Checkmate 057 – ITT)	[redacted]
Pembrolizumab	5.0 (KEYNOTE-010)	[redacted]	14.9 (KEYNOTE-010)	[redacted]

Abbreviations: ITT: intent-to-treat; mOS: median overall survival; mPFS: median progression free survival; PD-L1: programmed death-ligand 1

Due to the median PFS and OS not yet having been reached in LIBRETTO-001 for the SAS1 (first line group), it was not possible to conduct external validation of first line model outcomes for selpercatinib against trial data.

B.3.11 *Interpretation and conclusions of economic evidence*

The results of the cost-effectiveness analysis demonstrate that compared to all comparators across both the first and setting line settings, selpercatinib is associated with an extension to life and an improvement in HRQoL, as illustrated by the accrual of a greater number of QALYs and LYG across all comparisons. This is reflective of the results of the LIBRETTO-001 trial, which demonstrated that selpercatinib is a highly efficacious treatment in patients with *RET* fusion-positive advanced NSCLC, generating an elevated and durable tumour response. Nevertheless, the results of this analysis are considered to be conservative, and likely underestimate the true benefits that selpercatinib may bring to patients treated in the NHS in England and Wales, as described further below. Furthermore, the results of the current economic analysis are presented at the list price for selpercatinib, with ICER estimations anticipated to reduce [redacted].

The pairwise analysis between selpercatinib and nintedanib plus docetaxel is highlighted in particular. The results of this analysis illustrate that selpercatinib is associated with an OS estimate of [redacted] months versus [redacted] months for nintedanib plus docetaxel; a substantial difference of [redacted] months. The OS estimate for nintedanib plus docetaxel is further considered to be overly optimistic, for example, results of the LUME-Lung 1 trial[82] for nintedanib plus docetaxel report a median OS of just 12.6 months. It is therefore likely that the end of life criteria are met for this comparison.

The cost-effectiveness analysis is associated with several strengths, the first being that many new therapies for NSCLC, including those in the first and second line settings, and those targeting genetic alterations, have been appraised by NICE. A review of relevant NICE appraisals 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 ERG and Committee preferences for methodological approaches in this area, such as cost and resource use and the selection of HSUVs.

In addition, the results of the analysis may be considered generalisable to the UK. As discussed in Section B.2.12**Error! Reference source not found.**, the patient population of the LIBRETTO-001, the data for which inform the economic model, was considered to be representative of patients in UK clinical practice. Furthermore, the analyses in both the first and second line settings compare selpercatinib to treatment regimens used frequently in NHS clinical practice, as supported by a UK market share study conducted by Eli Lilly and Company, and feedback provided by clinicians practising in the UK. The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of selpercatinib into NHS clinical practice.

Furthermore, as noted previously, selpercatinib is a first-to-market therapy for *RET* fusion-positive NSCLC patients, and as such, there is currently little published data with regards to the natural history and prognosis of such patients. However, in order to overcome this, innovative use of data available from the Flatiron CGDB database was performed in order to understand long-term survival outcomes in real-world *RET* fusion-positive patients.

The model further closely aligns to the NICE reference case, being set from an NHS and PSS perspective, utilising a lifetime time horizon to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5%.

The key limitations of the analysis include the single-arm nature of the LIBRETTO-001 trial and the immaturity of the data currently available from the trial. As discussed in Sections B.2.8 and B.3.3, in order to connect selpercatinib to NMAs in the first and second line settings, it was necessary to generate a pseudo-control arm for each treatment line, which was subsequently used as a reference arm in the survival analysis for the cost-effectiveness model. The reference arms were adjusted for *RET* fusion-positive status through application of a time acceleration factor generated through use of data from the Flatiron database, and adjustment for other prognostic factors through the TMLE process. As discussed in Section B.3.10, it is likely that through this process, the PFS and OS estimates generated for the reference arms and comparators relevant to the decision problem have been overestimated, particularly for second line comparators. As suggested by Offin and colleagues, the response to immunotherapies of patients in this population may be particular low, highlighting the need for a targeted therapy for the tumours with a *RET* oncogenic driver. Accordingly, whilst it is very likely the full survival benefits that selpercatinib may bring to patients is not wholly reflected in this analysis, efforts were made, guided by feedback from an expert oncologist practising in the NHS, to select survival extrapolations with the greatest clinical plausibility as possible.

With regards to the immaturity of the survival data from LIBRETTO-001, particularly in the first line setting, as described above, efforts were made through use of the Flatiron database to gain an understanding of the long-term prognosis of *RET* fusion-positive NSCLC patients. As noted above, it is possible that resulting analyses have generated overly-conservative cost-effectiveness results for selpercatinib. Nevertheless, the LIBRETTO-001 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 in patients who have not received prior therapy for metastatic *RET* fusion-positive NSCLC, which is planned to enrol ~250 participants. The primary endpoint is PFS by IRC and the study includes a comparator arm of pembrolizumab combination therapy. It is therefore planned for preliminary clinical effectiveness and safety data for selpercatinib versus a comparator relevant to the decision problem 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 and PFS would be available prior to evaluation for exit of the CDF.

In conclusion, these results illustrate the benefits that selpercatinib may bring to patients newly diagnosed with advanced *RET* fusion-positive NSCLC through the newly established Genomic Hubs, as well as patients with either rapidly advancing disease or whose tumour biopsy was initially insufficient to yield a *RET* fusion-positive result, who have already been treated with other therapies.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for RET fusion-positive advanced non-small cell lung cancer [ID3743]

Clarification questions

November 2020

File name	Version	Contains confidential information	Date
ID3743_Selpercatininb NSCLC_Clarification Questions_Response [REDACTED]	NA	Yes	12th November 2020

Notes for company

Highlighting in the template

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

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Section A: Clarification on effectiveness data

LIBRETTO-001 trial

A1. Priority question: Are the versions of the trial protocol (version 8.0, dated 10 May 2019) and the statistical analysis plan (version 1.0, dated 8 August 2019), that are available as supplementary material to the Drilon et al 2020 publication, the most up to date versions of the LIBRETTO-001 trial protocol and statistical analysis plan? If more recent versions are available, please provide them.

The trial protocol (version 8.0; 10.05.2019) and statistical analysis plan (version 1.0; 08.08.2019) that are available as supplements to the Drilon et al. 2020 publication,[1] are the most up-to-date versions of the LIBRETTO-001 trial reports of the December 2019 data cut-off.

A2. Priority question: If available, please provide a clinical study report, or equivalent, for the most recent interim analysis (data cut-off date 16th December 2019, enrolled in LIBRETTO-001 as of 17th June 2019 enrolment date).

A Summary of Clinical Efficacy (ID 2.7.3; 13.07.2020) and Summary of Clinical Safety (ID 2.7.4; 19.08.2020) report for the most recent interim analysis (data cut-off: 16th December 2019) for LIBRETTO-001 have been provided alongside this document.

A3. Priority question: Please provide LIBRETTO-001 trial EORTC-QLQ-C30 data separately for the first-line SAS1 trial population, the second-line PAS trial population and the second-line IAS trial population.

Data presented in Document B, Section B.2.5.3 relate to the second-line Integrated Analysis Set (IAS) population. European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30 (EORTC-QLQ-C30) results were also collected and analysed in the Supplemental Analysis Set 1 (SAS1) population. The Primary Analysis Set (PAS) was a subpopulation within the IAS, but no specific analysis for the PAS population was performed for this outcome. Data from the IAS population were the main source of data for second line patients, and these data were used to inform the economic model, while data from the PAS were not.

EORTC-QLQ-C30 results for rearranged during transfection (*RET*)-fusion positive NSCLC patients in the SAS1 (first line) population who had both baseline and corresponding post-baseline assessments (N=27) are presented below in Table 1. In general, across subscales and cycle numbers, the proportion of patients who improved was greater in the SAS1 set compared to the IAS, however, such a comparison should be conducted with caution due to the comparatively low patient numbers in the SAS1 population compared to the IAS. [redacted].

Table 1. EORTC-QLQ-C30: Proportion of patients in the SAS1 population 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
Global health status/QoL	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]

	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Pain	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	N	[redacted]	[redacted]	[redacted]	[redacted]
	Improved	[redacted]	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; QoL: quality of life.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut-off).[2]

Generation of pseudo-control arms for the network meta-analyses (NMAs)

A4. Priority question: Please explain the company rationale for choosing to use data from the control arm of the REVEL trial in the second-line NMAs (rather than control arms of any of the other trials included in the second-line NMAs) to generate the selpercatinib pseudo-control arm.

Data from the control arm of the REVEL trial were selected for use in the second line network meta-analysis (NMA), as this trial was completed by Eli Lilly and Company, meaning individual patient data (IPD) were available for the analysis.[3] Control arm IPD were not available from any other trials included in the second line NMA. Using IPD in the analysis allowed Eli Lilly and Company to calculate more robust relative efficacy estimates.

Flatiron data could not be used, as the number of *RET*-fusion positive patients included within the database was too small to be able to divide them by comparator treatments of interest for use in calculating relative efficacy estimates.

A5. Priority question: Please clarify how many patients from the control arm of the REVEL trial were used to generate the pseudo control arm for the second-line NMAs, and whether any patients originally randomised to the control arm of the REVEL trial were excluded. If any patients were excluded, please provide reasons.

There were 625 patients allocated to the placebo plus docetaxel arm in the REVEL trial and 618 received assigned treatment.[3] Of these patients, 451 were confirmed to have non-squamous histology and were used to generate the pseudo control arm for the second line NMA. This differs from the number of patients with non-squamous histology that received placebo plus docetaxel reported in Garon (2014)[3] (n=447) as four patients, originally assigned ramucirumab plus docetaxel, were switched to placebo plus docetaxel. These four patients were also used to generate the pseudo control arm for the second line NMA.

A6. Priority question: Please clarify how many patients from the Flatiron CGDB database were included in the multivariable analysis outlined in Part 1 of the process to a generate pseudo-control arm (CS, Appendix D.1.7, p77-81) for the second-line NMAs of OS and PFS.

[redacted] *RET* fusion-positive NSCLC patients were identified within the Flatiron Clinico-Genomic database (CGDB), of which [redacted] patients had received first line and second line treatment. There were [redacted] *RET*-negative NSCLC patients that received first line and second line treatment. Both cohorts (*RET*-positive [n=[redacted]] and *RET*-negative [n=[redacted]]) were used to estimate a time acceleration factor for *RET* fusion-status in the second line treatment setting. These numbers differ to those presented and included in the multivariable analysis in the Company Submission, Appendix D.1.7, pp77 because they exclude patients with ALK, ROS1, BRAF and KRAS positive mutations.

A7. Priority question: Please clarify how much missing data for the relevant prognostic factors included in the multivariable analyses were imputed and exactly which imputation method(s) were used (CS, Appendix D.1.7, p78).

There were [redacted] patients in the Flatiron CGDB second line population. The volume of missing data for prognostic covariates included in the multivariable analyses are presented in Table 2.

Table 2. Missing data for prognostic covariates included in the multivariable analyses

Covariate	Missing data (count)
Race	[redacted]
Disease stage	[redacted]
Smoking status	[redacted]
ECOG score	[redacted]

Histology	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group.

A multiple imputation technique was used to calculate plausible values for missing variables.[4] Alternative strategies are to exclude records with missing data, which risks removing informative data and reduces the power of the study, or model the missing data as a category, which may make the model difficult to interpret. Single imputation can also be used to replace missing data with a predicted value. However, this does not consider the uncertainty of what the missing value might be. Multiple imputation based on bootstrapping can be used to address this problem.

The multiple imputation procedure that was chosen (“`aregImpute`”) in the “`Hmisc`” R package used additive regression, bootstrapping and predictive mean matching in order to calculate plausible values for missing variables. In total, 100 imputed data sets were created. The “`aregImpute`” method takes all aspects of uncertainty in the imputations into account, by using the bootstrap to approximate the process of drawing predicted values from a full Bayesian predictive distribution. Different bootstrap resamples are used for each of the multiple imputations, and a flexible additive model is fitted on a sample with replacement from the original data and this model is used to predict all of the original missing and non-missing values for the target variable. Splines with 3 knots were assumed for continuous predictors.

The default method of predictive mean matching was used, which works for categorical as well as continuous predictors. Predictive mean matching matches the predicted values from incomplete observations with predicted values from complete potential donor observations, where the latter predictions are based on the imputation model least squares parameter estimates. Further information on this imputation method is available from: https://www.rdocumentation.org/packages/Hmisc/versions/4.4-1/topics/aregImpute.

A8. Priority question: TMLE method, described in CS, Appendix D.1.7, p81

a. **Please clarify how the survival targeted minimum loss-based estimation (TMLE) method was used to adjust the RCT data for the control arm from the REVEL trial to match the LIBRETTO-001 trial. (CS, Appendix D.1.7, p81). Please also clarify how the TMLE method adjusts the data from the selpercatinib arm (CS, Figure 18 and Figure 25).**

The “`survtmle`” package in R was used to conduct targeted minimum loss-based survival analysis. This function estimates the marginal cumulative incidence for failures of specified types using targeted minimum loss-based estimation (TMLE), which is a general framework for constructing asymptotically linear and efficient substitution estimators of low-dimensional target parameters in rich infinite-dimensional models.[5] The simpler default settings were used for the analysis; more complex methods, such as using machine learning, can be performed but likely require larger samples. An introduction to this package can be found here: https://benkeser.github.io/survtmle/articles/survtmle_intro.html

The TMLE procedure uses covariate adjustment from a logistic regression by estimating a series of iterated covariate-conditional means.[5] The final iterated covariate-conditional mean is marginalised over the empirical distribution of baseline covariates to obtain an estimate of the marginal cumulative incidence.

The survival TMLE method uses the covariate data in two studies (REVEL control arm and LIBRETTO-001) to adjust survival estimates to produce two counterfactual average survival curves. It does not adjust the control arm from the REVEL trial to match the LIBRETTO-001 trial, but instead adjusts both arms to create a new counterfactual data set.

b. The reference provided for the TMLE method (Kreif et al 2016) refers to targeted maximum likelihood estimation, rather than targeted minimum loss-based estimation. Please clarify which TMLE method was used and provide any additional references that relate specifically to targeted minimum loss-based estimation.

As described in the response to part a, the "`survtmle`" package in R was used to conduct targeted minimum loss-based survival analysis. This function estimates the marginal cumulative incidence for failures of specified types using TMLE. Eli Lilly and Company refer the Evidence Review Group (ERG) to the three references listed below for further information on the targeted minimum-loss based survival analysis method; Benkeser (2018) has been supplied alongside this response document:[6, 7]

Benkeser D, Carone M, Gilbert PB. Improved estimation of the cumulative incidence of rare outcomes. Statist. Med. 2018; 37:280–93.

Benkeser D, Hejazi. survtmle: Targeted minimum loss-based estimation for survival analysis in R. 2017. https://github.com/benkeser/survtmle.URL http://dx.doi.org/10.5281/zenodo.835868.

Carone M, Diaz I, van der Laan M. High-order Targeted Minimum Loss-based Estimation. University of California Berkeley Division of Biostatistics Working Paper Series (Paper 331). 2014; 1–41.

A9. In addition to the R^2 model fit statistics for the multivariable parametric survival models (CS, Table 32), please provide adjusted R^2 statistics and predictive R^2 statistics for each survival model fitted for PFS and OS.

Example R code for generating adjusted and predictive R^2 statistics can be found here: https://gist.github.com/tomhopper/8c204d978c4a0cbcb8c0

The acceleration failure time models based on multiple imputed data, referred to in Table 32 in the CS, all include the same number of parameters (i.e. all models contained the same covariates and only varied according to the distribution: Weibull, log-normal, log-logistic). Each of these distributions is described by two parameters. "Adjusted R^2" is a method that enables models with different numbers of parameters to be compared with each other, unlike "R^2" which does not adjust for the number of parameters.

For a model based on multiple imputed data:

Adjusted $R^2 = 1 - (1 - R^2)(n-1)/(n-k-1)$,

where n is the number of non-missing values and k is the effective number of degrees of freedom (it should be noted that the number of non-missing values will vary for each imputed data set).

The link to the example code is for a general linear model without multiple imputation. This is different to a survival model based on multiple imputed data and the code is not applicable for the type of model fitted. However, the R^2 statistic that is outputted automatically by the "`fit.mult.impute`" procedure in the "`Hmisc`" package is appropriate for this situation. Predictive discrimination can be assessed by computing the Somers' D_{xy} rank correlation, which is also outputted automatically by the "`fit.mult.impute`" procedure. This can be used to assess overfitting and so compare models with different numbers of parameters. However, this is not needed in this situation as the models all contain the same number of parameters.

In summary, the adjusted R^2 statistic does not add anything beyond the R^2 statistic, when models are being compared with the same complexity, and the adjusted R^2 statistic is not easily generalisable to models fitted using multiple imputation. We conclude that when models of the same complexity are being compared, the R^2 statistic is sufficient.

An alternative would be to estimate Akaike information criterion (AIC) statistics for each imputed data set and then look at the proportion of times each model gives the best fit. This would seem a reasonable approach if models varied in complexity. However, considering the models have identical complexity we believe comparing R^2 values is sufficient.

A10. Please clarify that the reason why "ORR was not estimated for a RET-fusion control arm" (CS, Appendix D.1.7, p81) was because ORR data were not available from the Flatiron CGDB database? Or please provide an alternative reason.

Objective response rate (ORR) data were not available from the Flatiron CGDB database. A simple approach was initially considered whereby the Flatiron CGDB data would be used to predict ORR for an average patient from the LIBRETTO-001 trial and from the REVEL control arm. However, this was not feasible as response data in the Flatiron CGDB were only recorded among patients receiving targeted therapies; no data were available for chemotherapy only. As a result, data for response to docetaxel treatment was not available and so it was not possible to predict response rates for the REVEL control arm.

NMA methods

A11. Priority question: Please clarify whether the LIBRETTO-001 trial primary analysis set (n=105) or integrated analysis set (n=185) was used in the second-line NMAs.

Data from the IAS of the LIBRETTO-001 trial were used in the second line NMA.

A12. Priority question: Please provide a reference or further description of the 'hierarchical exchange model' (CS, Section 2.8.2, p108) used in the second-line NMAs of PFS and OS.

Hierarchical exchangeable models allow treatment effects to vary by covariates independently of the other treatments in the network of evidence. The treatment effect remains constant for any treatment not specified within a hierarchical exchangeable structure.[8] The methodology used in the second line NMAs of progression-free survival (PFS) and overall survival (OS) for the submission followed the methods presented in Vickers et al. (2019):[8]

Vickers AD, Winfree KB, Cuyun Carter G, Kiiskinen U, Jen MH, Stull D, Kaye JA, Carbone DP. Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis. BMC Cancer. 2019 Apr 15;19(1):353.

Please note that the model used in this submission was narrower than the model used in Vickers et al. (2019),[8] as efficacy of second line treatments was only allowed to vary by programmed death ligand-1 (PD-L1) expression in the submission, rather than by epidermal growth factor receptor (EGFR) mutation status, histology and PD-L1 expression as in Vickers et al. (2019).[8]

The original methodological publication for hierarchical modelling is Owen (2015)[9]:

Owen RK, Tincello DG, Abrams K. Network meta-analysis: development of a three-level hierarchical modelling approach incorporating dose-related constraints. Value Health. 2015;18:116-26.

A13. Priority question: Please clarify the company rationale for conducting meta-regression to adjust for baseline risk as well as adjustments for age, race, ECOG status and sex for the second-line NMAs (CS, Appendix D.4.7, p150-154, Table 38 and Table 39).

As described in NICE Decision Support Unit (DSU) technical support document 3 (TSD3), meta-regression is a technique used to address the presence of heterogeneity between studies in meta-analyses.[10] Meta-regression is used to relate the size of a treatment effect obtained from a meta-analysis to certain numerical characteristics of the included trials, with the aim of explaining some, or all, of the observed between-trial heterogeneity. These characteristics can be due to specific features of the individual participants in the trial, or they can be directly due to the trial setting or conduct.

In line with the approach taken in the Vickers et al. study,[8] for the analyses presented in the CS, meta-regression was used to explore the following study level covariates, which were included one at a time to see if they improved model fit: mean age, proportion of patients with Eastern Cooperative Oncology Group (ECOG) score ≥ 1, proportion of patients who were male, and proportion of Asian patients. These covariates were selected as each represents a prognostic factor in *RET*-fusion positive NSCLC (please see Section B.1.3 of the CS for a description of prognostic factors in *RET*-fusion positive NSCLC). Both random- and fixed-effect models were explored, and a hierarchical exchangeable model was used to take into account PD-L1 expression. The models, with or without the inclusion of covariates, were assessed for model fit, and the models with best fit for OS, PFS and ORR, as per DIC, were applied. Model fit statistics for the models explored in the second line NMA including adjustments for age, proportion of Asian patients, proportion of male patients and ECOG status are included in Table 3. Lower Deviance information criterion (DIC) values represent better model fit; as such an FE hierarchical exchangeable model adjusted for age was selected for OS and PFS, and a FE hierarchical exchangeable model adjusted for the proportion of Asian participants was used for ORR.

Table 3. DIC statistics for OS, PFS and ORR based on either fixed- or random-effects models with individual covariates

Covariate	DIC		
	OS	PFS	ORR
FE – no covariates	[redacted]	[redacted]	[redacted]
RE – no covariates	[redacted]	[redacted]	[redacted]
FE – hierarchical exchange model	[redacted]	[redacted]	[redacted]
FE – hierarchical exchange model + age	[redacted]	[redacted]	[redacted]
FE – hierarchical exchange model + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + age	[redacted]	[redacted]	[redacted]
FE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + ECOG	[redacted]	[redacted]	[redacted]
FE + proportion of male participants	[redacted]	[redacted]	[redacted]
RE + age	[redacted]	[redacted]	[redacted]
RE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
RE + ECOG	[redacted]	[redacted]	[redacted]
RE + proportion of male participants	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion; ECOG: Eastern Cooperative Oncology Group; FE: fixed-effect; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RE: random-effects.

[a] The hierarchical exchange structure was applied only to the model that was found to have the lowest DIC values with covariate adjustments. Hence, the DIC value for fixed effects hierarchical exchange with age is available for OS and PFS while the DIC value for fixed effect hierarchical exchange with Asian participants is available for ORR.

[b] models with convergent issues

A14. Priority question: Please clarify whether any investigations of inconsistency or incoherence relating to the direct and indirect evidence were conducted for connected NMAs (i.e., ORR, PFS and OS in the second-line overall population). If such investigations were carried out, please provide details.

A statistical test for inconsistency in an NMA can be monitored when a closed loop, not composed only by data from multi-arm trials, is formed within the network.[11] An assessment of inconsistency between direct and indirect evidence in the network was conducted for connected NMAs using a frequentist approach. The comparability of direct and indirect evidence for ORR, PFS and OS for the second line NMA is presented in Table 4, Table 5 and Table 6, respectively. Information on the comparability of direct and indirect evidence was not available for any comparators relevant to the decision problem in the second line NMA, as there were no closed loops within the network involving such comparators. However, direct and indirect evidence available for other comparisons in the NMA show that the analysis was robust, as in the majority of cases there was no statistically significant difference (p>0.05) observed between the indirect and direct comparisons.

Table 4. Split of direct and indirect evidence for ORR in the second line treatment population (fixed effects; frequentist)

Comparison	Number of studies	Proportion of direct evidence	NMA	Direct	Indirect	Difference (direct-indirect)	z (difference)	p-value (difference)
Erlotinib:Erlotinib + pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed:Erlotinib + pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMA: network meta-analysis; ORR: objective response rate.

Table 5. Split of direct and indirect evidence for PFS in the second line treatment population (fixed effects; frequentist)

Comparison	Number of studies	Proportion of direct evidence	NMA	Direct	Indirect	Difference (direct-indirect)	z (difference)	p-value (difference)
Docetaxel:Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel:Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Erlotinib + pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib + pemetrexed:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMA: network meta-analysis; PFS: progression-free survival.

Table 6. Split of direct and indirect evidence for OS in the second line treatment population (fixed effects; frequentist)

Comparison	Number of studies	Proportion of direct evidence	NMA	Direct	Indirect	Difference (direct-indirect)	z (difference)	p-value (difference)
Docetaxel:Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel:Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Erlotinib:Erlotinib + pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib + pemetrexed:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib:Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NMA: network meta-analysis; OS: overall survival.

A15. Priority question: It is stated (CS, Appendix D.1.6, p73):

"Given there was no clear violation in the PH assumption across the majority of studies connecting to the network, the NMA was conducted by synthesising HRs representing the treatment effects, assuming constant hazards as the base case."

Please justify the assumption of constant hazards as the base case given that the PH assumption was shown not to hold for three studies for PFS and two studies for OS in the second-line NMAs (CS, Appendix D.4.5, p139, Table 36).

The three studies included in the original NMA that showed evidence of proportional hazards violation for PFS were:

- Borghaei et al. 2015,[12] which included nivolumab and docetaxel
- Garon et al. 2014,[3] which included ramucirumab and docetaxel
- Neal et al. 2016,[13] which included erlotinib and cabozantinib

The two studies that showed evidence of proportional hazards violation for OS were:

- Borghaei et al. 2015,[12] which included nivolumab versus docetaxel
- Neal et al. 2016,[13] which included erlotinib and cabozantinib

Accordingly, of all studies that showed evidence of violating proportional hazards, only one study (Borghaei et al. 2015) included a comparator relevant to the decision problem (nivolumab).[12] In addition, this proportional hazards violation was only statistically significant in PD-L1<1% patients for OS, which is a subgroup not considered as part of this submission. For these reasons, it was deemed acceptable to conduct the NMA through synthesising hazard ratios (HRs) and assuming constant hazards.

Nevertheless, given that some evidence of proportional hazards violation was found, an NMA that adopted a fractional polynomial approach was explored as a scenario analysis. Due to the immaturity of selpercatinib OS data from LIBRETTO-001, particularly in comparison to the data available for comparators to selpercatinib, it was not deemed appropriate to conduct such an NMA for OS. However, an NMA was conducted using this method for PFS. Both a one- and two-dimensional fractional polynomial approach was explored. The network diagram for the PFS fractional polynomials NMA is presented in Figure 1.

Figure 1. PFS network diagram (fractional polynomials method)

[redacted]

Abbreviations: BID: Twice per day; PFS: progression-free survival.

The DIC results representing the model fit for each of the one- and two-dimensional models are presented in Table 7. Based on the DIC statistics, the two-dimensional model provided a better model fit than the one-dimensional model.

Table 7. DIC statistics for the one- and two-dimension fractional polynomial models for PFS

Power p1	Power p2	Dbar	Dhat	pD	DIC
One-dimension fractional polynomial					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-dimensional fractional polynomial					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion.

The results of the fractional polynomials (one-dimensional) NMA for PFS is presented in Figure 2 whilst the results of the two-dimensional model is shown in Figure 3.

The results of the two dimensional model (Figure 3) show that selpercatinib is associated with the greatest PFS of all interventions up to approximately 15 months, after which point long-term PFS predictions are similar to nintedanib plus docetaxel, which is not expected to be a clinically valid result. The flattening of the curve occurs from the point at which no data are available. This model was selected however, as it shows the best fit for the short-term data within the follow-up period of each trial. In order to estimate the long-term survival for comparators, constant HRs based on the reference arm (docetaxel) were applied in order to generate data to inform the cost-effectiveness model. As the survival curve for docetaxel also flattens, a conservative approach of assuming constant hazards from the maximum trial follow-up time for docetaxel, and applying this to extrapolate was utilised. The docetaxel arm uses the hazard in the last model cycle before the end of the Kaplan-Meier data for the remainder of the time horizon. For all other interventions, after the end of the Kaplan-Meier data for that intervention, the anchored hazard for docetaxel is applied for the remainder of the time horizon.

Figure 2. PFS over time for each of the interventions as obtained first order fractional polynomial (p1 = [redacted]) network meta-analysis model

[redacted]

Abbreviations: BID: Twice per day; PFS: progression-free survival.

Figure 3. PFS over time for each of the interventions as obtained second order fractional polynomial (p1 = [redacted], p2 = [redacted]) network meta-analysis model

[redacted]

Abbreviations: BID: Twice per day; PFS: progression-free survival.

Scenario cost-effectiveness analyses were run using this anchored fractional polynomial approach to extrapolate survival data. Results of these scenario analyses are presented in **Error! Reference source not found.**Table 8 and Table 9 for 'all patients' and patients with PD-L1≥1%, respectively. It should be noted that PFS results for atezolizumab and pembrolizumab were assumed to equal nivolumab in the PD-L1≥1% population as atezolizumab and pembrolizumab were not included in the PFS NMA second order fractional polynomial network. Using the anchored fractional polynomial approach to estimate survival resulted in a reduction of the pairwise ICERs for selpercatinib versus all comparators compared with the base case ICERs originally presented in the CS (please see CS Section B.3.7.1 for base case results).

Table 8. Model results with anchored fractional polynomial second line RET fusion-positive NSCLC (all patients): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 9. Model results with anchored fractional polynomial second line *RET* fusion-positive NSCLC (PD-L1≥1%): list price

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

A16. In addition to the DIC statistics provided for the second-line NMAs (CS, Appendix D4.7, p150-154, Table 38 and Table 39), please also provide the posterior mean of the residual deviance for each NMA.

Based on discussions on the clarification call with the ERG, we understand that this question related to the first line population, which is no longer being considered in the submission. DIC statistics for the second line NMAs are available in the Company Submission, Appendix D4.7, Table 38 and Table 39, while the posterior mean of the residual deviance for each NMA are also presented in these tables, in the column marked 'Dbar'.

A17. In the studies included in the NMAs where a HR was not reported or could not be estimated:

a. Please clarify which studies were included in the second-line NMAs of OS and PFS according to the methodology of Woods et al 2010, using "other commonly reported survival statistics" (CS, Appendix D.1.6, p73 and Appendix D.4.7, p145).

b. Please also clarify which studies used in the second-line NMAs of OS and PFS estimated the cumulative hazard in each trial arm from count data (CS, Appendix D4.7, 146).

Where a HR was not reported or could not be estimated, median survival data in months from Kim et al. 2016[14] (study of pemetrexed versus gefitinib) for both OS and PFS were included in the second line NMA according to the methodology of Woods et al. 2010.[15] No studies in the second line NMA estimated the cumulative hazard in each trial arm from count data.

A18. Please clarify why ORR is modelled by 'categories' using a binomial model in the second-line NMA (CS, Appendix 4.7, p148) rather than as binary data (i.e., the proportion of patients who experienced a response).

Thank you for highlighting this error. ORR was modelled as binary data in the second line NMA.

NMA results

A19. Priority question: Please provide relative treatment effects (ORs or HRs with 95% CrIs) for selpercatinib versus:

a. docetaxel plus placebo (i.e., the pseudo control arm), nivolumab (PD-L1≥1%), and nintedanib + docetaxel in the second-line treatment population from the NMAs of ORR, OS and PFS

b. pembrolizumab (PD-L1≥1%) in the second-line treatment population from the NMAs of OS and PFS

c. atezolizumab in the second-line treatment population from the NMA of OS.

The relative treatment effects (HRs) for selpercatinib versus comparators, based on a fixed effects hierarchical exchangeable model adjusted for age (OS and PFS) and adjusted for the proportion of Asian patients (ORR), is presented in Table 10. Results indicate that selpercatinib is associated with improved survival outcomes (OS and PFS) and ORR versus all comparators considered in the submission. Selpercatinib demonstrated significant improvements in OS versus: (1) docetaxel plus placebo and (2) nintedanib plus docetaxel. Selpercatinib demonstrated significant improvements in PFS versus all comparators, where data were available. Selpercatinib also demonstrated significant improvements in ORR versus: (1) docetaxel plus placebo and (2) nintedanib plus docetaxel.

Table 10. Relative treatment effects (HRs and 95% credible intervals [CrI]) for selpercatinib versus comparators based on a fixed hierarchical exchangeable model and adjusted for age (OS and PFS) or the proportion of Asian patients (ORR)

Selpercatinib versus:	Docetaxel + placebo	Nivolumab (PD-L1≥1%)	Nintedanib + docetaxel	Pembrolizumab (PD-L1≥1%)	Atezolizumab
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	NA
ORR	[redacted]	[redacted]	[redacted]	NA	NA

Footnotes: [a] Fixed hierarchical exchangeable model adjusted for age; [b] Fixed hierarchical exchangeable model adjusted for the proportion of Asian patients; * Significant association.

Abbreviations: CrI: credible interval; HR: hazard ratio; NA: not applicable; PFS: progression-free survival; ORR: objective response rate; OS: overall survival.

Source: Eli Lilly and Company Ltd. Data on File.[16]

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide primary analysis LIBRETTO-001 trial PFS, OS and TTD K-M data (from the PAS and IAS datasets) for patients with non-squamous NSCLC whose prior therapies included the following:

- **An immunotherapy but not a multi-kinase inhibitor (MKI)**
- **An MKI but not an immunotherapy**
- **An MKI and an immunotherapy**
- **Neither an immunotherapy nor an MKI.**

Please present analysis outputs using the format of the sample table.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Primary analysis PFS, OS and time-to treatment discontinuation (TTD) Kaplan-Meier (KM) data from the IAS dataset is provided for two subgroups: "prior immunotherapy" and "no prior immunotherapy". Separate data for the PAS dataset is not presented, as this is a subpopulation of the IAS dataset and has not been used to inform the cost-effectiveness analysis. Data has not been provided for MKI therapy as division by MKI and immunotherapy produces patient subsets whose sample size is small and therefore underpowered, as well as immature, making a statistically meaningful analysis of survival endpoints uninformative.

Prior immunotherapy

KM data for OS, PFS (PFS data by Independent Assessor assessment) and TTD in IAS patients that received prior immunotherapy are presented in Table 11, Table 12 and Table 13, respectively. The KM plots of OS, PFS and TTD are presented in Figure 4, Figure 5 and Figure 6, respectively. The median OS was [redacted], the median PFS was [redacted] months and the median TTD was [redacted] months. The median PFS was slightly lower in the IAS prior immunotherapy subgroup, compared with the whole IAS population ([redacted]; CS, Document B, Section B.2.5.2, Table 20). In the whole IAS population, [redacted] (CS, Document B, Section B.2.5.2, Table 21). Differences between the IAS population and the prior immunotherapy subgroup may relate to the smaller sample size, and therefore lower statistical power, of the subgroup.

Table 11. Kaplan-Meier OS data for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Figure 4. Kaplan-Meier plot of OS for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy

[redacted]

Note: Censored patients denoted by "ǀ".
Abbreviations: IAS: Integrated Analysis Set; OS: overall survival; NSCLC: non-small cell lung cancer.

Table 12. Kaplan-Meier PFS data for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy (independent assessor)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]				[redacted]	[redacted]

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
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[redacted]				[redacted]	[redacted]

Figure 5. Kaplan-Meier plot of PFS for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy

[redacted]

Note: Censored patients denoted by "I".
Abbreviations: IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progression free survival.

Table 13. Kaplan-Meier TTD data for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
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Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
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Figure 6. Kaplan-Meier plot of TTD for second line (IAS) *RET* fusion-positive NSCLC patients that received prior immunotherapy

[redacted]

Note: Censored patients denoted by "I".

Abbreviations: IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; TTD: time to treatment discontinuation.

No prior immunotherapy

KM data for OS, PFS (PFS data by Independent Assessor assessment) and TTD, in IAS patients that did not receive prior immunotherapy are presented in Table 14, Table 15 and Table 16, respectively. The KM plots of OS, PFS and TTD are presented in Figure 7, Figure 8 and Figure 9, respectively. The median OS was [redacted], the median PFS was [redacted] months and the median TTD was [redacted] months. Median OS and PFS were greater in the subgroup that did not receive prior immunotherapy compared with those IAS patients that did receive prior immunotherapy, and were the same as the outcomes for the IAS population as a whole (CS, Document B, Section B.2.5.2, Tables 20 and 21). Median TTD for the "no prior immunotherapy subgroup" was the same as those patients that received prior immunotherapy.

Table 14. Kaplan-Meier OS data for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]				[redacted]	[redacted]

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
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[redacted]				[redacted]	[redacted]
[redacted]				[redacted]	[redacted]

Figure 7. Kaplan-Meier plot of OS for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy

[redacted]

Note: Censored patients denoted by "ǀ".
Abbreviations: IAS: Integrated Analysis Set; OS: overall survival; NSCLC: non-small cell lung cancer.

Table 15. Kaplan-Meier PFS data for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy (independent assessment)

Days	Survival	Failure	Survival Standard Error	Number Failed	Number Left
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]
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[redacted]				[redacted]	[redacted]
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Figure 8. Kaplan-Meier plot of PFS for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy

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Note: Censored patients denoted by "I".

Abbreviations: IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progression free survival.

Table 16. Kaplan-Meier TTD data for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy

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Figure 9. Kaplan-Meier plot of TTD for second line (IAS) *RET* fusion-positive NSCLC patients that did not receive prior immunotherapy

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Note: Censored patients denoted by "I".

Abbreviations: IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; TTD: time to treatment discontinuation.

Section C: Textual clarification and additional points

Systematic literature review methods

C1. Regarding the SLR, please tell us how many independent reviewers were involved in data extraction and how many were involved in quality assessment.

Data extraction and data quality checking was performed for 116 trials (306 individual publications). Each trial was extracted by one reviewer and extracted data were quality checked independently by a different reviewer. A total of 10 reviewers were involved with the data extraction and quality checking of the extracted data for the 306 individual publications.

Trial quality assessments were undertaken by three reviewers. Two reviewers performed the assessments, and one reviewer performed an independent quality check.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

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]

NICE National Institute for Health and Care Excellence

2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	Medical Director
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of 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 carers to include in your submission?	As a result of the COVID pandemic, our contact with patients and carers has 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.

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. There are currently no NICE recommended treatments, specifically for RET fusion positive lung cancer patients. 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, 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 being assessed for RET positive lung cancer. • Oral therapy. • Data shows systemic and intracranial response. •	

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Selpercatinib for *RET* fusion-positive advanced non-small cell lung cancer [ID3743]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 133177

Completed 9th December 2020

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Janette Greenhalgh	Critical appraisal of the clinical evidence
Tosin Lambe	Summary of the economic evidence
Yenal Dundar	Critical appraisal of the clinical evidence, including search strategies
Joanne McEntee	Critical appraisal of the company submission
Lynn Campbell	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
IAS	Integrated Analysis Set
ICER	Incremental cost-effectiveness ratio
IRC	Independent Review Committee
LYG	Life years gained
MKI	Multi-kinase inhibitor
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OSAS	Overall Safety Analysis Set
PAS	Patient Access Scheme
PFS	Progression-free survival
PrAS	Primary analysis set
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QLQ	Quality of life questionnaire
RANO	Response assessment in neuro-oncology criteria

RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RET	Rearranged during transfection (*italics* indicate the gene encoding the RET protein)
RET	Transmembrane receptor tyrosine kinase encoded by the *RET* gene
ROS-1	C-ros oncogene 1
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SLR	Systematic literature review
TEAE	Treatment emergent adverse event
TMLE	Targeted minimum loss-based estimation

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred modelling assumptions and the resulting incremental cost effectiveness results. The ERG highlights that, given the uncertainty around the survival projections for all treatments, the cost effectiveness results generated by the ERG are not robust; they should only be considered as being more reflective of the available evidence than the results generated by the company.

Section 1.2 provides an overview of the key issues identified by the ERG. The modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained are provided in Section 1.3. The key issues identified by the ERG are explained in more detail in Section 1.4 to Section 1.7. The key differences between the company and the ERG's preferred modelling assumptions are presented in Section 1.7. Background information on the condition, the technology and the evidence and information on non-key issues are presented in Section 2 to Section 7 of the main ERG report.

All the issues outlined in this report have been identified by the ERG; they do not represent NICE's opinion.

1.1 *Overview of the ERG's key issues*

Table 1 Summary of key issues

ID3743	Summary of issue	Report sections
1	Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	Section 2.5 and Section 3.2
2	LIBRETTO-001 trial survival events and length of follow-up	Section 2.5.5, Section 3.2.4, Section 3.3.1, Section 3.3.2 and Section 3.7
3	Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice	Section 2.5.2 and Section 3.2.3
4	Relevant comparator treatments	Section 2.5.4 Section 6.1.2
5	The relevance of population participating in the trials that provided comparator evidence for the company NMAs	Section 3.6.1
6	Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	Section 3.6 and Appendix **Error! Reference source not found.**
7	The company modelling of survival for patients receiving selpercatinib	Section 6.3
8	The company modelling of survival for patients receiving nintedanib+docetaxel	Section 6.3.2 and Section 6.3.3
9	Progressive disease health state utility value	Section 6.4.1
10	Costing of treatment with selpercatinib	Section 6.4.2
11	Cost of testing for *RET* fusions	Section 6.4.3
12	NICE End of Life criteria may not be met	Section 7
13	Absence of data for subgroups of patients listed in the final scope issued by NICE	Section 2.5

NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; RET=rearranged during transfection

1.2 *Overview of key model outcomes*

NICE Technology Appraisals compare how much a new technology improves length (overall survival [OS]) and quality of life (measured in QALYs). An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

All company base case results (generated using list prices for all drugs) show that treatment with selpercatinib is more expensive than any of the comparator treatments. Further, as health state utility values do not vary by treatment, and patients receiving selpercatinib are modelled to live longer than patients who receive any of the comparator drugs, treatment with selpercatinib is always associated with higher QALYs than any of the comparator drugs.

The selection of different distributions used to extrapolate LIBRETTO-001 trial OS data had the biggest impact on the size of the company base case ICERs per QALY gained no matter the comparator. For example, for the comparison of selpercatinib versus nintedanib+docetaxel, the base case ICER per QALY gained varied by between -30.92% and 765.19% depending on which distribution was chosen to model survival for patients receiving selpercatinib. Other influential parameters for this comparison were the weights (by treatment) applied to progression-free and progressed-disease health state utility values.

1.3 *The decision problem: summary of the ERG's key issues*

Issue 1 Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial

Report section	Section 2.5 and Section 3.2
Description of issue and why the ERG has identified it as important	The LIBRETTO-001 trial is a single-arm trial and, therefore, does not provide data that facilitate a direct comparison of the effectiveness of selpercatinib versus any comparator treatment
What alternative approach has the ERG suggested?	No alternative approach was suggested by the ERG. The company has carried out NMAs to generate clinical effectiveness results for comparator treatments
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing The ERG acknowledges that the selpercatinib data provided by the company from the LIBRETTO-001 trial are the only selpercatinib data available for previously treated patients with *RET*+ NSCLC

ERG=Evidence Review Group; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; RCT=randomised controlled trial; *RET*=rearranged during transfection

Issue 2 LIBRETTO-001 trial survival events and length of follow-up

Report section	Section 2.5.5, Section 3.2.4, Section 3.3.1, Section 3.3.2 and Section 3.7
Description of issue and why the ERG has identified it as important	The small number of LIBRETTO-001 trial survival events [redacted] and short median follow up times [redacted] mean that there is considerable uncertainty around the impact of selpercatinib on survival
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	The effect on company base case results of modelling using more mature LIBRETTO-001 trial data is not known. Whilst K-M data from a later data cut would reduce the uncertainty around the company OS and PFS projections for patients receiving selpercatinib, uncertainty around the relative effectiveness of selpercatinib versus comparator treatments would remain unknown
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing The ERG acknowledges that the selpercatinib data provided by the company from the LIBRETTO-001 trial are the only selpercatinib data available for previously treated patients with *RET*+ NSCLC

ERG=Evidence Review Group; IAS=integrated analysis set; K-M=Kaplan-Meier; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection; RCT=randomised controlled trial

Issue 3 Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice

Report section	Section 2.5.2 and Section 3.2.3
Description of issue and why the ERG has identified it as important	The company cost effectiveness results relate to patients treated in the second-line setting. However, the company has **not** provided separate clinical effectiveness results for patients who have **only** received prior chemotherapy or for patients who have **only** received prior immunotherapy. [redacted] patients (IAS) in the LIBRETTO-001 trial had received prior platinum chemotherapy [redacted] had also received an anti-PDL1 therapy [redacted] and [redacted] had received an MKI [redacted] Furthermore, the ERG notes that MKIs are not listed as prior treatment options in the current NICE recommended treatment pathway
What alternative approach has the ERG suggested?	Whilst the company could provide effectiveness results for the subgroup of patients who had only received prior chemotherapy, this was not a pre-specified subgroup in the LIBRETTO-001 trial and, given the small size of this subgroup and the small number of survival events, the value of these data is uncertain
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Further data are required to show if patients who received PDC and immunotherapy (IAS, [redacted]) received these treatments consecutively or simultaneously. Any additional information describing prior treatments that will help NICE to assess the generalisabilty of the LIBRETTO-001 trial results to the NHS would be helpful

ERG=Evidence Review Group; IAS=integrated analysis set; MKI=multi-kinase inhibitor; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; PDC=platinum doublet chemotherapy; RCT=randomised controlled trial; *RET*=rearranged during transfection

Issue 4 Relevant comparator treatments

Report section	Section 2.5.4 and Section 6.1.2
Description of issue and why the ERG has identified it as important	**Non-squamous patients** The company cost effectiveness results relate to patients treated with selpercatinib in the second-line setting versus pembrolizumab, nivolumab, atezolizumab and nintedanib+docetaxel. Clinical advice to the ERG is that the relevant comparators to selpercatinib in the second-line setting in the NHS are nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC as most NHS patients receive an immunotherapy as a first-line treatment and therefore would not be offered an immunotherapy as a second-line treatment Whilst some NHS patients may receive immunotherapy in the second-line setting, the ERG considers that these patients make up a relatively small proportion of patients treated in this setting. In addition, the company has applied HRs from NMAs to a pseudo-control (reference arm) to generate model survival estimates for all comparators. The ERG considers that the NMAs are methodologically flawed due to uncertainties associated with the data inputs and the generation of the pseudo-control (reference) arm and therefore the NMA results are not sufficiently robust for decision making The NICE scope lists docetaxel, pemetrexed+carboplatin, and PDC as relevant comparators to selpercatinib; the company has not provided cost effectiveness results for these treatment options. However, the ERG has generated scenario results for selpercatinib versus docetaxel
What alternative approach has the ERG suggested?	The ERG's critique of the company's cost effectiveness analyses has focused on the cost effectiveness of selpercatinib versus nintedanib+docetaxel and versus docetaxel
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing

ERG=evidence review group; HR=hazard ratio; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; PDC=platinum doublet chemotherapy; RCT=randomised controlled trial; *RET*=rearranged during transfection

1.4 *The clinical effectiveness evidence: summary of the ERG's key issues*

Issue 5 The relevance of populations participating in the trials that provided comparator evidence for the company NMAs

Report section	Section 3.6.1
Description of issue and why the ERG has identified it as important	The patients participating in the trials included in the networks (other than the LIBRETTO-001 trial) were not tested for *RET*+ fusion status. As the incidence of *RET* fusions is between 1% to 2% of all NSCLC cases, it is likely that the populations in the trials that provided comparator evidence only included small numbers of patients with *RET*+ NSCLC. Furthermore, the networks were not adjusted for any prognostic factors associated with *RET*+ NSCLC
What alternative approach has the ERG suggested?	The ERG considers that use of alternative NMA approaches, such as matching-adjusted indirect comparisons, would not reduce uncertainty; the inherent uncertainty relating to the populations and the pseudo-control arm would remain
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing

ERG=Evidence Review Group; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; *RET*=rearranged during transfection; RCT=randomised controlled trial

Issue 6 Uncertainty associated with the use of a pseudo-control arm to connect selpercatinib for network meta-analysis

Report section	Section 3.6 and Appendix 9.2
Description of issue and why the ERG has identified it as important	The company has used a pseudo-control (reference) arm to connect selpercatinib (LIBRETTO-001 trial) data to the OS and PFS networks. Due to inherent uncertainties associated with the generation of the pseudo-control (reference) arm, the ERG considers that definitive conclusions regarding the direction and magnitude of effect of selpercatinib versus comparators cannot be made
What alternative approach has the ERG suggested?	The ERG considers that the use of alternative NMA approaches, such as matching-adjusted indirect comparisons, would not reduce uncertainty; the inherent uncertainty relating to the populations and the pseudo-control arm would remain
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	The following information would provide more clarity on the TMLE method used by the company: i) how does the use of the TMLE method benefit the data in this context? ii) what is being adjusted in the TMLE method? iii) what do the adjusted data reflect that the data before the TMLE adjustment did not reflect? iv) what is the 'counterfactual' survival time in this context? A scenario using NMA results without TMLE adjustment (i.e., using the pseudo-control arm data with only multivariable analysis adjustments using Flatiron data) would also provide more clarity regarding whether the TMLE method may have resulted in the overestimation of treatment effects in the pseudo control arms. However, the inherent uncertainty relating to the populations and the pseudo-control arms would not be resolved by provision of this additional evidence

ERG=Evidence Review Group; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; *RET*=rearranged during transfection; TMLE= target minimum loss estimation

1.5 *The cost effectiveness evidence: summary of the ERG's key issues*

Issue 7 Company modelling of survival for patients receiving selpercatinib

Report section	Section 6.3
Description of issue and why the ERG has identified it as important	The company has ignored AIC and BIC rankings and selected distributions to model OS and PFS for patients receiving selpercatinib based on advice from one clinician who considered that the most important criterion driving choice of distribution was that the relative advantage of selpercatinib over the pseudo-control (reference) arm should be maintained across the whole model time horizon. The ERG considers that this approach is subjective, arbitrary and open to significant bias
What alternative approach has the ERG suggested?	For the comparison of selpercatinib versus nintedanib+docetaxel and versus docetaxel, the ERG adopted a different approach (see Section 6.3.3 for full details of ERG survival estimation methods)
What is the expected effect on the cost-effectiveness estimates?	Using the ERG's survival modelling approach significantly increases the ICER per QALY gained for the comparison of selpercatinib versus nintedanib+docetaxel (and versus docetaxel)
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing Further evidence from clinicians, with reference to their experience of treating patients with *RET*+ NSCLC, would be helpful. Specifically, what proportion of patients with advanced *RET*+ NSCLC who received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with selpercatinib as a second-line treatment? The ERG acknowledges that the incidence of *RET*+ NSCLC is between 1% and 2% of all NSCLC cases and that the experience of NHS clinicians may be limited

AIC=Akaike information criterion; BIC=Bayesian information criterion; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; RCT=randomised controlled trial; *RET*=rearranged during transfection

Issue 8 Company modelling of survival for patients receiving comparator treatments

Report section	Section 6.3.2 and Section 6.3.3
Description of issue and why the ERG has identified it as important	The company adjusted the pseudo-control (reference) arm data using HR results from the company OS and PFS NMAs. Due to the ERG's uncertainties associated with the data inputs and with the generation of the pseudo-control (reference) arm data in the OS and PFS NMAs, the ERG considers that company OS and PFS projections (based on NMA results) for all comparator treatments are unreliable
What alternative approach has the ERG suggested?	For the comparison of selpercatinib versus docetaxel, the ERG has assumed that the survival of patients receiving docetaxel is equivalent to the survival represented by the pseudo-control (reference) arm. For the comparison of selpercatinib versus nintedanib+docetaxel, the ERG has made the same assumption but has also included an additional QALY gain to represent the added benefit of nintedanib+docetaxel compared with docetaxel monotherapy. The ERG has not generated alternative cost effectiveness results for selpercatinib versus any of the other comparators
What is the expected effect on the cost-effectiveness estimates?	Using the ERG's survival modelling approach significantly increases the ICER per QALY gained for the comparison of selpercatinib versus nintedanib+docetaxel
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators that are relevant to NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing Further evidence from clinicians, with reference to their experience of treating patients with *RET*+ NSCLC, would be helpful. Specifically, what proportion of patients with advanced *RET*+ NSCLC who received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with nintedanib+docetaxel or docetaxel as second-line treatments? The ERG acknowledges that the incidence of *RET*+ NSCLC is between 1% and 2% of all NSCLC cases and that the experience of NHS clinicians may be limited

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; RCT=randomised controlled trial; *RET*=rearranged during transfection

Issue 9 Progressive disease health state utility value

Report section	Section 6.4.1
Description of issue and why the ERG has identified it as important	The utility values used in the company model are those used in the base case analysis presented in NICE TA484; however, the PD health state utility value used by the company is higher than the PD value that the NICE TA484 AC considered was most appropriate
What alternative approach has the ERG suggested?	The ERG considers that if it is appropriate to use utility values from TA484, then the values used should be those preferred by the AC
What is the expected effect on the cost-effectiveness estimates?	Using the NICE TA484 AC preferred PD health state utility value increases the ICER per QALY gained for the comparison of selpercatinib versus nintedanib+docetaxel
What additional evidence or analyses might help to resolve this key issue?	EQ-5D-3L data should be collected directly from patients with *RET*+ NSCLC

AC=Appraisal Committee; EQ-5D=EuroQol Five Dimensions; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; PD=progressed disease; QALY=quality adjusted life year; *RET*=rearranged during transfection; TA=Technology Appraisal

Issue 10 Costing of treatment with selpercatinib

Report section	Section 6.4.2
Description of issue and why the ERG has identified it as important	The company has used LIBRETTO-001 trial PFS data as the basis for costing treatment with selpercatinib
What alternative approach has the ERG suggested?	The ERG considers that as TTD data are available from the LIBRETTO-001 trial these data should be used to estimate the cost of treatment with selpercatinib
What is the expected effect on the cost-effectiveness estimates?	Using TTD data, rather than PFS data, to cost treatment with selpercatinib increases the ICER per QALY gained for the comparison of selpercatinib versus nintedanib+docetaxel
What additional evidence or analyses might help to resolve this key issue?	Estimates of the cost of treatment with selpercatinib will become more reliable as more mature data from the LIBRETTO-001 trial become available

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Issue 11 The cost of testing for *RET* fusions has not been included in either the company or ERG cost effectiveness analyses

Report section	Section 6.4.3
Description of issue and why the ERG has identified it as important	The company states that testing for *RET* fusions will be an absorbed cost. However, *RET* fusions are not routinely tested for in the NHS and a national NHS Genomic Medicine Service to provide NGS has yet to be established
What alternative approach has the ERG suggested?	Costs associated with testing for *RET* fusions in the interim period (until NGS is established) should be included in the cost effectiveness estimates
What is the expected effect on the cost-effectiveness estimates?	Whilst the magnitude of the impact on cost effectiveness results of including the cost of RET fusion testing cannot be determined, the exclusion of testing costs is exerting downward pressure on the ICER per QALY gained for the comparison of selpercatinib versus any comparator
What additional evidence or analyses might help to resolve this key issue?	This issue will only be resolved when the cost of testing for *RET* fusion mutations is known Any information on the cost of testing for RET fusions would help to generate more accurate cost effectiveness results

ICER=incremental cost effectiveness ratio; NGS=Next Generation Sequencing; NSCLC=non-small cell lung cancer; QALY=quality adjusted life year; *RET*=rearranged during transfection

1.6 *Other key issues: summary of the ERG's view*

Issue 12 NICE End of Life criteria may not be met

Report section	Section 7
Description of issue and why the ERG has identified it as important	The company considers that, based on results from their model, for the comparison of treatment with selpercatinib versus nintedanib+docetaxel: • median and mean OS for patients receiving nintedanib+docetaxel are [redacted] respectively • median and mean OS for patients receiving selpercatinib are [redacted], respectively, resulting in estimated median and mean extensions to life delivered by selpercatinib, when compared with nintedanib+docetaxel, of [redacted] respectively
What alternative approach has the ERG suggested?	Using the ERG alternative OS projections for patients treated with selpercatinib and nintedanib+docetaxel: • implementing the ERG preferred modelling of OS for patients receiving nintedanib+docetaxel generates mean OS of [redacted] (median not evaluable) • whilst results from the company model suggest that the OS gain for patients receiving selpercatinib could exceed 3 months, without more robust comparative OS data this gain is highly uncertain
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators and previous treatments that are relevant for NHS patients with pre-treated, advanced *RET*+ NSCLC is required to determine, with any degree of certainty, whether the NICE End of Life criteria have been met for this group of patients

ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; OS=overall survival; RCT=randomised controlled trial; *RET*=rearranged during transfection

Issue 13 Absence of data for subgroups of patients listed in the final scope issued by NICE

Report section	Section 2.5
Description of issue and why the ERG has identified it as important	The company did not provide any clinical or cost effectiveness evidence for patients with squamous disease (any setting) The company provided clinical and cost effectiveness evidence for patients with non-squamous disease (first-line setting). However, 2 weeks following the submission of the CS to NICE, the company made the decision to limit their focus for this appraisal to pre-treated patients with non-squamous disease
What alternative approach has the ERG suggested?	Clinical advice to the ERG is that it was reasonable for the company to exclude patients with advanced squamous NSCLC because *RET*+ fusions are very rare in this population
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares selpercatinib with comparators and previous treatments that are relevant for NHS patients with pre-treated, advanced *RET*+ NSCLC would provide the optimal data for decision making. A trial of this design is not currently ongoing

CS=Company Submission Document B; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer; *RET*=rearranged during transfection

1.7 *Summary of ERG's preferred assumptions and resulting ICER*

Given the uncertainty around the survival projections for all treatments considered, the cost effectiveness results generated by the ERG are not robust; they should only be considered to be more reflective of the available evidence than the results generated by the company.

Table A Cost effectiveness results: selpercatinib versus nintedanib+docetaxel (list prices)

Scenario	Incremental cost	Incremental QALYs	ICER per QALY gained	Change from company base case
Company approach				
A. Company's base case	[redacted]	[redacted]	[redacted]	
ERG alternative approach				
B1. Discounting starting at start of year two	[redacted]	[redacted]	[redacted]	[redacted]
B2. Remodelling OS for selpercatinib and nintedanib+docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
B3. TA484 AC preferred PD health state utility value	[redacted]	[redacted]	[redacted]	[redacted]
B4. Use of TTD rather than PFS data to estimate cost of treatment with selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]
Alternative ERG base case (B1-B4)	[redacted]	[redacted]	[redacted]	[redacted]

AC=Appraisal Committee; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PD=progressive disease; PFS=progression-free survival; QALY=quality adjusted life year; TA=Technology Appraisal; TTD=time to treatment discontinuation

Table B Cost effectiveness results: selpercatinib versus docetaxel (list prices)

Scenario*	Incremental cost	Incremental QALYs	ICER per QALY gained
Alternative ERG base case (B1-B4) but without any life year gain/QALY added	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*The company did not provide cost effectiveness results for the comparison of selpercatinib versus docetaxel

The ERG's critique of the company model is described in Section 6.2 to Section 6.4 of the ERG report. Details of the ERG's alternative approach to assessing cost effectiveness of selpercatinib versus nintedanib+docetaxel and versus docetaxel are provided in Section 6.5 of the ERG report.

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

The focus of this appraisal is on the use of selpercatinib as a treatment for adults with advanced (Stage IIIB to Stage IV), rearranged during transfection fusion-positive non-small cell lung cancer (*RET*+ NSCLC) who require systemic therapy after disease progression. Within this Evidence Review Group (ERG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission.

Two patient populations are discussed in the CS: (i) patients with advanced *RET*+ NSCLC who are treatment naïve and (ii) patients with advanced *RET*+ NSCLC who have progressed after treatment. The company did not consider patients with advanced squamous disease. Two weeks following submission of the CS to the National Institute for Health and Care Excellence (NICE) the company made the decision to limit their focus for this appraisal to patients with advanced, non-squamous *RET*+ NSCLC who have progressed after treatment (i.e., pre-treated patients).

2.2 *RET fusion-positive NSCLC*

Lung cancer is the third most common cancer in England; 38,906 people were diagnosed in England in 2017.[1] Lung cancer is the most common cause of cancer-related death in England;[1] in 2017, the age standardised mortality rate for women and men was 46.1 per 100,000 and 65.8 per 100,000, respectively.[1]

Lung cancer is categorised into non-small cell lung cancer (NSCLC), which accounts for around 80% to 85% of all lung cancer cases in England,[2] and small cell lung cancer.[3] NSCLC is further categorised into two main histological types: non-squamous type carcinomas and squamous type cell carcinomas.[4] Non-squamous type carcinoma represents around 70% of all NSCLC cases[3] and can be divided into two main histological subtypes: adenocarcinoma (40% of all NSCLC cases) and large cell carcinoma (10% to 15% of all NSCLC cases).[4]

NSCLC can be further classified by testing for genetic markers that have been identified as oncogenic drivers. These include epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements[5] and *RET* fusions.[6] Patients with *RET*+ NSCLC represent 1% to 2% of all NSCLC cases.[6] *RET* fusion mutations most commonly occur in adenocarcinomas but have also been identified in tumours of mixed histology[6] and are rare in squamous NSCLC.[7,8]

RET is a transmembrane receptor tyrosine kinase that is expressed by multiple tissue types, including lung, adrenal medulla and thyroid.[6] In healthy people, RET protein is involved in cell growth, cell division and cell differentiation.[9] Abnormal activity of RET protein in cancer is caused by mutations and fusions to the gene (*RET*) encoding the RET protein. Gene fusions are the most common type of mutation to occur to the *RET* gene in NSCLC. *RET* fusions are typically caused by inversion of the short and long arms of chromosome 10 that leads to fusion of the *RET* intracellular kinase domain to a partner gene.[10] The most common fusion partner is KIF5B which accounts for 50% to 70% of all *RET* fusions.[6] *RET* fusions are oncogenic drivers because the fusions result in increased activity of the RET kinase domain that then leads to increased activation of downstream signalling pathways involved in cell survival, proliferation, migration and angiogenesis.[6,11]

Patients with *RET*+ NSCLC have similar characteristics to patients with NSCLC who have other oncogenic drivers.[6] Patients with *RET*+ NSCLC or other oncogenic drivers are usually aged ≤60 years and most often have either never smoked or are former smokers.[12] Patients with *RET*+ NSCLC rarely express more than one oncogenic driver.[13] There are no studies that have investigated the prevalence or demographic characteristics of patients with *RET*+ NSCLC in the UK. The IMMUNOTARGET retrospective registry study[12] included 16 patients with advanced *RET*+ NSCLC from Europe, US, Israel and Australia. Two-thirds (66.7%) of patients in this study had never smoked, only 6.7% were current smokers, and the median age was 54.5 years (range: 29 to 71 years). Evidence from a meta-analysis[14] of nine epidemiological studies (including 6899 patients with NSCLC and 84 patients with *RET*+ NSCLC) that was undertaken to evaluate the correlation between the presence of the *RET* fusion gene with demographic and clinical characteristics of people with NSCLC, suggests that *RET* fusions are more common in women than men, and in people of Asian ethnicity than in people of non-Asian ethnicity.

The prognosis for patients with NSCLC is dependent on disease stage at diagnosis. Nearly half (46.8%) of patients with NSCLC are diagnosed with Stage IV[15] disease and the 1-year survival rate for these patients is 40%.[3] The IMMUNOTARGET registry study[12] reported, for patients with *RET*+ NSCLC (16/551), a median progression-free survival (PFS) of 2.1 months for patients with *RET*+ NSCLC and a median overall survival (OS) of 21.3 months.

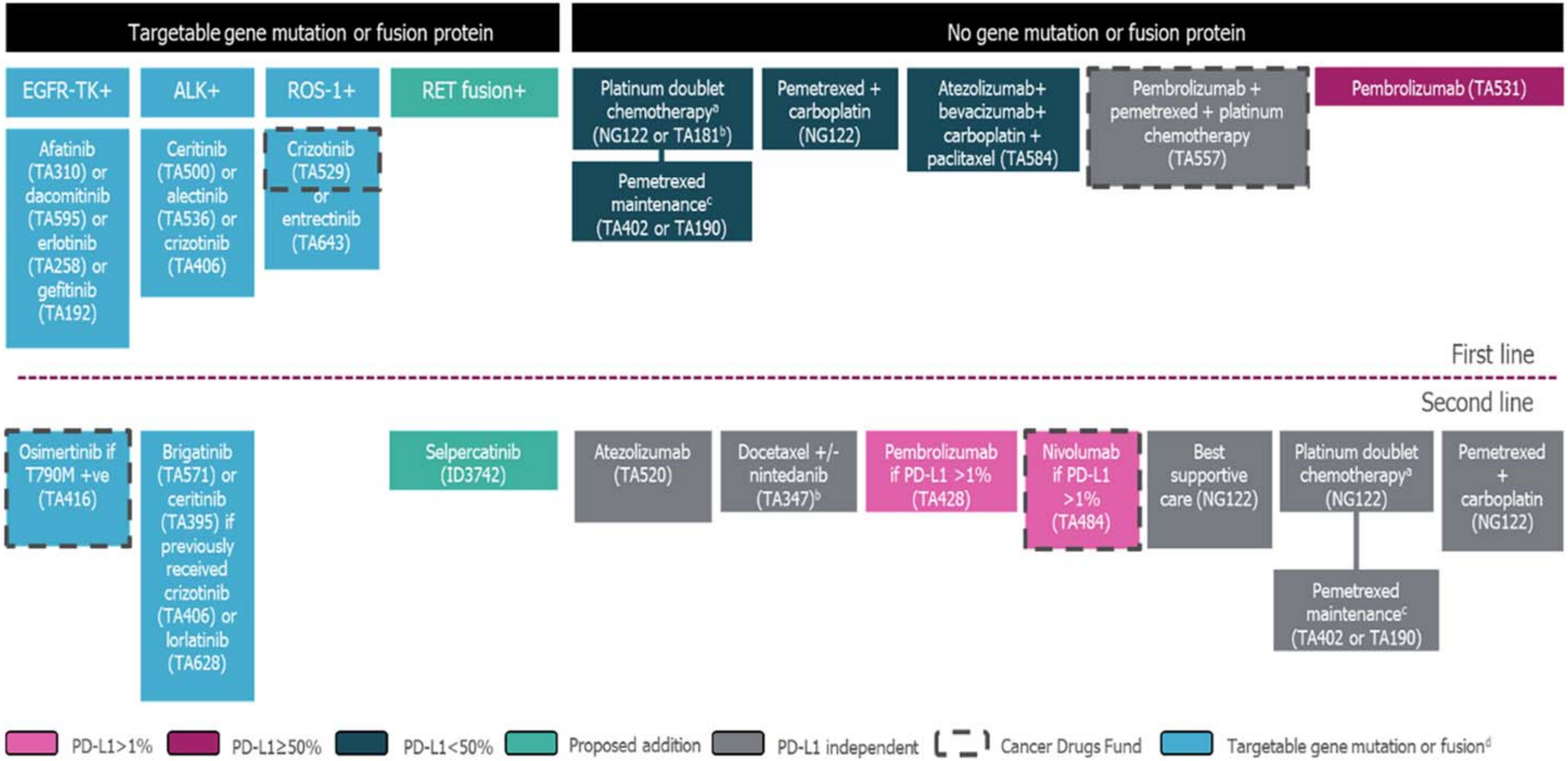
2.3 *Selpercatinib*

Selpercatinib is a selective kinase inhibitor;[16] it is the first kinase inhibitor to selectively target the RET tyrosine kinase receptor. Selpercatinib prevents the activation of fusion, mutant and wild type isoforms of RET and disrupts the signalling pathway to stop tumour cell survival, proliferation, migration and angiogenesis.

2.4 *Company's overview of current service provision*

2.4.1 Treatments in the pathway

The company representation of the current treatment pathway for patients with non-squamous, advanced *RET*+ NSCLC has been reproduced in Figure 1. The company's proposed positioning of selpercatinib is as a treatment option for patients with advanced, non-squamous *RET*+ NSCLC who have had prior treatment for their disease (i.e., pre-treated patients). Clinical advice to the ERG is that Figure 1 is an accurate reflection of NHS clinical practice for patients with non-squamous NSCLC.



[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 and adenocarcinoma, respectively.
[c]Pemetrexed maintenance is only permitted after pemetrexed + cisplatin (not carboplatin).
[d]Other targeted treatments are represented in the pathway for illustrative purposes but are not indicated for patients with *RET* fusion-positive NSCLC.
Abbreviations: ALK: anaplastic lymphoma kinase; EGFR-TK: epidermal growth factor receptor tyrosine kinase; PD-L1: programmed death-ligand; *RET*: rearranged during transfection; ROS-1; c-ros oncogene 1.

Figure 1 Current treatment pathway for patients with advanced, non-squamous NSCLC

Source: CS, Figure 4

First-line treatment

Clinical advice to the ERG is that first-line treatment for approximately 75% of patients with non-squamous NSCLC and no identified oncogenic driver is immunotherapy, given as monotherapy (usually pembrolizumab) or combined with chemotherapy (usually pembrolizumab with pemetrexed+carboplatin). Eligibility for treatment with specific immunotherapy agents depends on levels of programmed death-ligand 1 (PD-L1) expression (Table 1). Approximately 15% of patients will not receive immunotherapy because either immunotherapy is contraindicated or because patients are not fit enough to tolerate immunotherapy (performance status [PS] ≥2); these patients will receive chemotherapy. A further 10% of patients will only receive best supportive care.

Table 1 First-line treatment options for NSCLC (no oncogenic drivers) by PD-L1 status

First-line treatment	NICE guidance
PD-L1 TPS 0% to 49%	
Atezolizumab+bevacizumab+carboplatin+paclitaxel	TA584[17]
Platinum doublet chemotherapy (with or without pemetrexed maintenance)	NG122[5] (TA402[18] TA190[19])
Pemetrexed+carboplatin (adenocarcinoma or large cell carcinoma only)	TA181[20]
Pembrolizumab+pemetrexed+platinum (CDF only)	TA557[21]
PD-L1 TPS ≥50%	
Pembrolizumab	TA531[22]
Pembrolizumab+pemetrexed+platinum (CDF only)	TA557[21]

CDF=Cancer Drugs Fund; TPS=tumour proportion score; PD-L1=programmed death-ligand 1

Second-line treatment

Treatment options in the second-line setting depend on the patient's treatment history (Table 2). Clinical advice to the ERG is that patients who are treated with an immunotherapy as a first-line treatment will not receive an immunotherapy as a second-line treatment. Patients treated in the first-line setting with immunotherapy can receive nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin or PDC in the second-line setting. Patients who are treated with chemotherapy in the first-line setting, and who are fit enough, may receive immunotherapy (atezolizumab, nivolumab or pembrolizumab, depending on PD-L1 status) as a second-line treatment. Clinical advice to the ERG is that some patients will not be fit enough for any second-line treatment.

Table 2 Treatment options after first-line treatment for pre-treated NSCLC

<table>
<tr><th colspan="2">Treatment after progression on first-line treatment</th><th>NICE guidance</th></tr>
<tr><td colspan="3">PD-L1 TPS 0% to 49%</td></tr>
<tr><td colspan="2">Atezolizumab (no PDL expression)</td><td>TA520[23]</td></tr>
<tr><td colspan="2">Pembrolizumab (PD-L1≥1%)</td><td>TA428[24]</td></tr>
<tr><td colspan="2">Docetaxel</td><td>NG122[5]</td></tr>
<tr><td colspan="2">Nintedanib+docetaxel (adenocarcinoma histology only)</td><td>TA347[25]</td></tr>
<tr><td colspan="2">Nivolumab (PD-L1≥1% and CDF only)</td><td>TA484[26]</td></tr>
<tr><td colspan="3">PD-L1 TPS ≥50%</td></tr>
<tr><td rowspan="2">After pembrolizumab</td><td>Platinum doublet chemotherapy (with or without pemetrexed maintenance)</td><td>NG122[5] (TA402[18] TA190[19])</td></tr>
<tr><td>Pemetrexed+carboplatin (adenocarcinoma or large cell carcinoma only)</td><td>NG122[5]</td></tr>
<tr><td>After PDC or pemetrexed+carboplatin</td><td>Nintedanib+docetaxel (adenocarcinoma histology only)</td><td>TA347[25]</td></tr>
<tr><td>After pembrolizumab+ pemetrexed+platinum (CDF only)</td><td>Docetaxel</td><td>NG122[5]</td></tr>
</table>

CDF=Cancer Drugs Fund; PDC=platinum doublet chemotherapy; PD-L1=programmed death-ligand 1; TPS=tumour proportion score

Source: Extracted from NICE Guidance NG122[5]

2.4.2 Testing for *RET*+ NSCLC

The company reports that an accurate and validated assay is required to identify patients with *RET*+ NSCLC (CS, Table 2). The company is confident (CS, Table 1) that the transition to testing at Genomic Hubs using Next Generation Sequencing (NGS) will be established in England during the time period taken to process this appraisal. Clinical advice to the ERG was that routine testing of patients for *RET*+ NSCLC is not currently widely available in the NHS at any point in the treatment pathway; however, it would be feasible to introduce a test for *RET* fusion status alongside the panel of molecular tests already conducted at diagnosis (i.e., alongside EGFR, ROS1, ALK testing). If selpercatinib was recommended by NICE for use in the NHS as a second-line of treatment, testing for *RET* fusion status could be carried out at diagnosis, or it could be carried out on disease progression. Clinical advice to the ERG was that testing on progression could be carried out using a pre-existing tumour specimen, which would need to have been stored, or would require repeat biopsy, which may not be a procedure that patients wish to undertake.

2.4.3 Number of patients eligible for treatment with selpercatinib

In Document A of the CS (Table 23), the company has provided an estimate of the number of patients in England with RET+ NSCLC and an estimate for the proportion of these patients who would be eligible for treatment with selpercatinib. The company estimates that there would be 309 patients with RET+ NSCLC in Year 1, [redacted] patients of which would be eligible for treatment with selpercatinib in Year 1 and rising to [redacted] patients eligible for treatment in Year 5. The estimates include the use of selpercatinib as a first or subsequent line of treatment. The ERG estimates that 263 patients are likely to be diagnosed with advanced *RET*+ NSCLC in England annually (Table 3).

Table 3 ERG estimate of the annual number of cases of *RET*+ NSCLC in England

Estimated parameters	**Estimated number of patients**
Annual incidence of lung cancer in England in 2017[27]	38,906
Proportion of cases of lung cancer that are NSCLC=85%[2]	33,070
Proportion of cases on NSCLC that are of non-squamous histology=70%[28]	23,149
Proportion of patients diagnosed at Stage IIIB or Stage IV=57%[28]	13,194
Proportion of patients with *RET*+ NSCLC=2%[6]	263

NSCLC=non-small cell lung cancer; *RET*=rearranged during transfection

2.5 *Critique of company's definition of decision problem*

A summary of the decision problem outlined in the final scope[28] issued by NICE and addressed by the company is presented in Table 4. Each parameter is discussed in more detail in the text following Table 4 (Section 2.5.1 to Section 2.5.8).

Table 4 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Population	Patients with advanced *RET*+ NSCLC who require systemic therapy	Patients with advanced, non-squamous, pre-treated *RET*+ NSCLC who require systemic therapy	The company has limited their focus for this appraisal to pre-treated patients with non-squamous disease Clinical advice to the ERG is that the exclusion of patients with advanced, squamous NSCLC is reasonable as *RET* fusions occur infrequently in tumours of squamous histology Two weeks following submission of the CS to NICE, the company made the decision to limit their focus for this appraisal to pre-treated patients with non-squamous disease
Intervention	Selpercatinib	As per scope	As per scope

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Comparator(s)	**Pre-treated non-squamous NSCLC:** PD-L1 ≥50%: • Platinum doublet[b] • Pemetrexed+carboplatin • Docetaxel (for adenocarcinoma histology) ± nintedanib • Best supportive care PD-L1 <50% • Atezolizumab monotherapy • Atezolizumab+bevacizumab+carboplatin+paclitaxel (only after failed EGFR or ALK targeted treatment) • Pembrolizumab monotherapy • Nivolumab monotherapy • Docetaxel (for adenocarcinoma histology) ± nintedanib • Best supportive care	**Pre-treated non-squamous NSCLC:** • Pembrolizumab (PD-L1≥1%) • Nivolumab[c] (PD-L1≥1%) • Atezolizumab (all patients) • Docetaxel with nintedanib (all patients)	The four comparators considered by the company are recommended by NICE for use as second-line treatment options for patients with NSCLC. However, the ERG considers that only nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC are relevant comparators to selpercatinib (see Section 2.5.4 for discussion)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rate • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Objective response rate (ORR) • Duration of response (DOR) • PFS • OS • HRQoL (EORTC-QLQ-C30) • Adverse events (AEs)	Results for selpercatinib for all the listed outcomes are available from the single-arm LIBRETTO-001 trial. However, low numbers of OS and PFS events have occurred and therefore the true magnitude of these results is currently uncertain Data to allow comparison of the effectiveness of selpercatinib versus other treatments are generated by NMAs for the following outcomes: OS, PFS and ORR. The networks have been constructed by connecting LIBRETTO-001 trial data to comparator data via pseudo-control (reference) arms

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Economic analysis	The reference case stipulates that cost effectiveness should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and PSS perspective The availability of any commercial arrangements for selpercatinib, comparator and subsequent treatments will be taken into account. The availability of any managed access arrangement for selpercatinib will be taken into account The use of selpercatinib in NSCLC is conditional on the presence of RET gene fusion. The economic modelling should include the costs associated with diagnostic testing for RET in patients with advanced NSCLC cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test	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 QALY 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	The company has provided cost effectiveness results in the form of ICERs per QALY gained for the comparisons of selpercatinib versus nintedanib+docetaxel, atezolizumab, pembrolizumab (PD-L1 ≥1%) and nivolumab (PD-L1 ≥1%)
Subgroups	If evidence allows, a subgroup analysis will be performed by previous therapy. The availability and cost of biosimilar and generic products should be taken into account	First- and second-line patient populations	Two weeks following submission of the CS to NICE the company made the decision to limit their focus for this appraisal to **pre-treated** patients with non-squamous disease

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Special considerations including issues related to equity or equality	NA	In the technology appraisal of entrectinib for treating ROS1-positive advanced NSCLC (TA643)[29], concerns related to inequitable access to targeted treatments, due to regional variation in molecular testing practices, were discussed. In England, the transition to NGS testing, completed at Genomic Hubs, means it will be possible to test for *RET* rearrangements routinely alongside other oncogenic drivers in a standardised manner across different centres. As such, this equality consideration is not expected to be a concern in this submission	Clinical advice to the ERG is that, in the NHS, Next Generation Sequencing is not yet in operation and that testing for *RET* fusion mutations is not carried out routinely

[a] carboplatin or cisplatin
[b] cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel or vinorelbine
[c] NICE appraisal following Cancer Drugs Fund exit
AE=adverse event; ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; HRQoL=health-related quality of life; ICER=incremental cost-effectiveness ratio; NA=not applicable; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; PD-L1=programmed death-ligand 1; PSS=Personal Social Services; QALY=quality adjusted life year; *RET*=rearranged during transfection; ROS-1=c-ros oncogene 1; TPS=tumour proportion score
Source: Final scope[28] issued by NICE and CS, Table 1

2.5.1 Source of clinical effectiveness data

The company has presented clinical effectiveness evidence (CS, Section B2.2) from the single-arm LIBRETTO-001 trial.[30] This trial is an ongoing, multicentre, open-label, phase I/II trial. Phase I of the LIBRETTO-001 trial is a dose escalation phase while phase II is a dose expansion phase (see Section 3.2.2). Only clinical effectiveness evidence from phase II of the LIBRETTO-001 trial is relevant to the final scope[28] issued by NICE. The ERG highlights that it has been shown that treatment effects in phase II trials may be greater than those observed in phase III trials.[31]

The LIBRETTO-001 is a basket trial and includes patients with tumour types other than NSCLC (medullary thyroid cancer, colon cancer and any solid tumour cancer). [redacted] patients have been enrolled to date in the LIBRETTO-001 trial but, at the time of the interim analysis, only 200 of these patients had pre-treated, advanced *RET*+ NSCLC and had received selpercatinib as a second- or later-line treatment. Data from these 200 patients provide evidence relevant to the final scope[28] issued by NICE. Only evidence from 184 patients that received prior platinum chemotherapy were presented in the CS. However, median trial OS follow up for these patients that received prior platinum chemotherapy is only [redacted] and very few PFS and OS events have occurred.

2.5.2 Population

The company did not consider patients with advanced squamous disease; clinical advice to the ERG is that this focus is reasonable as *RET* fusion mutations rarely occur in NSCLC tumours with squamous histology.[7,8]

Intervention population

Clinical advice to the ERG is that it is difficult to be certain whether the characteristics of the LIBRETTO-001 trial population are representative of NHS patients with pre-treated, advanced *RET*+ NSCLC because very few patients have been identified as having *RET*+ NSCLC. However, clinical advice to the ERG is that the characteristics of the LIBRETTO-001 trial population are similar to those of patients with NSCLC expressing other oncogenic drivers, i.e., patients aged ≤60 years who, typically, have either never smoked or are former smokers.

The generalisability of the results from the LIBRETTO-001 trial to patients with *RET*+ NSCLC treated in the NHS may be limited because:

- The LIBRETTO-001 trial population had received between [redacted] prior treatments ([redacted])

- Approximately [redacted] of patients in the LIBRETTO-001 trial (integrated analysis set [IAS]) had received prior treatment with multi-kinase inhibitors (MKIs); MKIs are not recommended by NICE for patients with advanced *RET*+ NSCLC
- [redacted] had received prior platinum-based chemotherapy and [redacted] had also received prior immunotherapy. Clinical effectiveness evidence to support the treatment of patients with *RET*+ NSCLC in the second-line setting is only available from 184 patients ([redacted] patients had only received prior anti-PD-1 treatment and [redacted] patients had received prior MKIs). SAS2 (n=16) was not included in the CS as patients had received prior systemic therapy that did not include platinum-based chemotherapy

The ERG considers that the clinical effectiveness evidence presented in the CS is insufficient to demonstrate the clinical effectiveness of selpercatinib in the second-line setting as a treatment for *RET*+ NSCLC.

Comparator population

As the LIBRETTO-001 trial is a single-arm trial, the company performed NMAs to generate effectiveness evidence for the comparison of selpercatinib versus other treatments. However, the proportions of patients with *RET*+ NSCLC included in the trials that informed the NMAs is not known.

2.5.3 Intervention

The company has provided the following information about selpercatinib (CS, Table 2 and p25):

- Selpercatinib is a selective kinase inhibitor;[16] it is the first kinase inhibitor to selectively target the RET tyrosine kinase receptor. Selpercatinib prevents the activation of fusion, mutant and wild type isoforms of RET and disrupts the signalling pathway to stop tumour cell survival, proliferation, migration and angiogenesis[16]
- Selpercatinib does not currently have a marketing authorisation in the UK (CS, Table 2). On [redacted], the company submitted a conditional marketing authorisation application for selpercatinib for the treatment of advanced *RET*+ NSCLC to the European Medicines Agency (EMA). A decision from the EMA Committee for Medicinal Products for Human Use (CHMP) is expected in [redacted]
- Selpercatinib is administered orally and is available as 40mg and 80mg hard capsules.[16] The recommended dose is 160mg twice daily (BID).[16] The recommended dose reduction for patients experiencing intolerable adverse effects is 40mg.[16]

Genetic testing for *RET* fusion status

Genetic sequencing is required to identify *RET*+ NSCLC. The company reports (CS, p31) that NHS England is transitioning to a national NHS Genomic Medicine Service made up of seven

Genomic Laboratory Hubs, to standardise genomic testing across England and to provide Next Generation Sequencing.[32] *RET* rearrangements are listed in the National Genomic Test Directory for cancer; therefore, screening for *RET*+ NSCLC is planned to be routinely carried out during genomic sequencing for oncogenic drivers in cancer.[33] Clinical advice to the ERG is that, in the NHS, patients are not yet routinely tested for *RET* fusion status (see Section 2.4.2 of this ERG report).

2.5.4 Comparators

The company has provided indirect evidence to allow the comparison of the clinical effectiveness of selpercatinib with four of the nine comparators listed in the final scope[28] issued by NICE (pembrolizumab, nivolumab, atezolizumab and nintedanib+docetaxel). The company's reasons for excluding the other treatments listed in the final scope[28] issued by NICE and the ERG's comments, are provided in Table 5.

Table 5 Company rationale for excluding comparators from the company submission

Comparator	Company rationale	ERG comment
Platinum doublet therapy	The company's market share data indicate that platinum doublet chemotherapy has a small UK market share in the second-line treatment setting	The ERG considers that platinum doublet chemotherapy is a relevant comparator to selpercatinib in the second-line setting. Clinical advice to the ERG is that in the NHS, most (75%) patients are treated with an immunotherapy in the first-line setting. Patients who receive immunotherapy in the first-line setting are not treated with immunotherapy in the second-line setting. Clinical advice to the ERG is that patients whose disease progresses after treatment with an immunotherapy combined with chemotherapy are treated with nintedanib+docetaxel, docetaxel or PDC
Pemetrexed+ carboplatin	The company's market share data indicate that pemetrexed+carboplatin has a small UK market share in the second-line treatment setting	The ERG considers that pemetrexed+carboplatin is a relevant comparator to selpercatinib. Clinical advice to the ERG is that in the NHS, approximately three-quarters of patients are treated with an immunotherapy in the first-line setting and that patients who receive immunotherapy in the first-line setting are not treated with an immunotherapy in the second-line setting Patients who progress after treatment with an immunotherapy without chemotherapy are treated with pemetrexed+carboplatin
Docetaxel monotherapy	Clinical advice to the company was that docetaxel with nintedanib is preferentially used in clinical practice over docetaxel monotherapy and therefore docetaxel monotherapy is not a relevant comparator	Clinical advice to the ERG is that almost all patients who are suitable for treatment with docetaxel would be offered treatment with nintedanib+docetaxel. However, it is important to include docetaxel monotherapy as a comparator treatment as nintedanib+docetaxel is only recommended by NICE as an option for treating cancer of adenocarcinoma histology[25]
Atezolizumab with bevacizumab, carboplatin and paclitaxel	NICE guidance (TA584) recommends this treatment only after initial EGFR- or ALK-targeted treatments have failed. However, *RET*	Patients with *RET*+ NSCLC rarely express more than one oncogenic driver.[13]

	fusions tend to be mutually exclusive of other major lung cancer oncogenic drivers, and therefore this combination was not considered to be an appropriate comparator to selpercatinib	
Best supportive care	The company reports (CS, p20) that BSC is a treatment option for patients unfit for systemic therapy and therefore is not relevant to the population defined in the final scope[28] issued by NICE	Clinical advice to the ERG is that BSC would not be an appropriate treatment option for patients who require systemic treatment

ALK=anaplastic lymphoma kinase; BSC=best supportive care; CS=company submission; EGFR=epidermal growth factor receptor; ERG=Evidence Review Group; HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer; OS=overall survival; *RET*=rearranged during transfection
Source: Adapted from CS, Table 1

Clinical advice to the ERG is that approximately 75% of NHS patients are treated with an immunotherapy in the first-line setting; these patients are not treated with an immunotherapy in the second-line setting. Treatment with pembrolizumab, nivolumab or atezolizumab in the second- or later-line setting is, therefore, only relevant to patients who are treated in the first-line setting with platinum-based chemotherapy (approximately 15% of patients as 10% of patients would receive best supportive care).

The ERG considers that the most relevant comparators to selpercatinib are nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC. However, of these, the company has only presented evidence for the comparison of the effectiveness of selpercatinib versus nintedanib+docetaxel, and versus docetaxel from NMAs. The ERG highlights that the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a confirmed *RET*+ NSCLC population, nor have the networks been adjusted for the same prognostic factors associated with *RET*+ NSCLC listed in Appendix D.1.7 used to adjust the pseudo-control (reference) arm.

The ERG has identified a number of concerns about the methods used to generate the pseudo-control (reference) arms used in the NMAs and, therefore, considers that results from the NMAs do not provide a robust basis for decision making (see Section 3.6.5).

2.5.5 Outcomes

Clinical advice to the ERG is that the outcomes listed in the final scope[28] issued by NICE are the most relevant outcomes for patients with pre-treated, advanced *RET*+ NSCLC. Overall response rate (ORR) is the primary endpoint of the LIBRETTO-001 trial. The company also presented LIBRETTO-001 trial OS and PFS results. However, there are low numbers of OS and PFS events and therefore the true magnitude of these results is currently uncertain (Section 3.3.1 and Section 3.3.2).

Clinical advice to the ERG is that outcomes for patients with brain metastases, including intracranial PFS and intracranial ORR, are also of interest to clinicians. However, although the company assessed central nervous system (CNS) ORR and CNS duration of response (DOR) during the LIBRETTO-001 trial, these data are not available.

The company generated OS, PFS and ORR NMA results for selpercatinib versus the pseudo-control (reference) arm (docetaxel+placebo), nintedanib+docetaxel, atezolizumab, nivolumab and pembrolizumab.

2.5.6 Economic analysis

The company has carried out two sets of cost effectiveness analyses, depending on tumour PD-L1 expression level. For all patients, irrespective of tumour PD-L1 expression level, the company has compared the cost effectiveness of selpercatinib versus nintedanib+docetaxel and versus atezolizumab. For patients with PD-L1 ≥1%, the company has compared the cost effectiveness of selpercatinib versus nivolumab and pembrolizumab. Results are expressed in terms of incremental cost per quality adjusted life year (QALY) gained. These results were generated using list prices for all treatments. Outcomes were assessed over a lifetime horizon (25 years) and costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.5.7 Subgroups

No subgroups considered.

2.5.8 Other considerations

The company considers (CS, Table 44) that, for patients with pre-treated, advanced *RET*+ NSCLC, selpercatinib satisfies NICE End of Life criteria[34] versus nintedanib plus docetaxel. The ERG considers that the life expectancy criterion has not been met, and it is not certain that the life extension criterion has been met (Section 7).

The company [redacted]

If recommended for use in the NHS, selpercatinib would be the first targeted treatment available for patients with pre-treated, advanced *RET*+ NSCLC (CS, p25). The company states that they are actively seeking funding from the Cancer Drugs Fund (CDF) for selpercatinib in *RET+* NSCLC "…given the immaturity of the available survival data" (CS, p12).

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review*

Full details of the methods used by the company to identify and select clinically relevant evidence to demonstrate the effectiveness of selpercatinib for patients with pre-treated, advanced *RET*+ NSCLC are presented in the CS (Appendix D.4). The ERG did not find any relevant studies in addition to those identified by the company. An assessment of the extent to which the review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 6. The ERG has identified some minor issues (described in Table 6) but considers that these do not affect the quality and completeness of the evidence used to inform this appraisal.

Table 6 ERG appraisal of the company's systematic review methods

Review process	ERG response	ERG comments
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.4.2, Table 33
Were appropriate sources searched?	Yes	CS, Appendix D.4.1
Was the timespan of the searches appropriate?	Partially	Databases were searched from 01 January 2015 to 25 September 2019. Conference proceedings published up to 5 years prior to September 2019 were hand searched. The ERG has updated the company's database searches and found no further relevant publications
Were appropriate search terms used?	Yes	No additional ERG comments
Were the eligibility criteria appropriate to the decision problem?	Partially	Only publications relevant to patients with non-squamous NSCLC were included in the company's systematic review. Patients with non-squamous disease are a subset of the patient population specified in the final scope[28] issued by NICE. As noted in Section 2.5.2 of this report, the ERG considers that the exclusion of patients with squamous NSCLC is reasonable
Was study selection applied by two or more reviewers independently?	Yes	No additional ERG comments
Was data extracted by two or more reviewers independently?	Partially	In response to question C1 of the clarification letter, the company confirmed that one reviewer extracted data and the extractions were checked by a second, independent reviewer. The ERG considers that this is an acceptable strategy
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company used the CASP checklist[35] for cohort studies. For the identified RCTs, the company used the criteria recommended by the CRD[36] at the University of York. For details of the company risk of bias assessment, please see CS, Appendix D.4.10
Was the quality assessment conducted by two or more reviewers independently?	Yes	In response to question C1 of the clarification letter, the company confirmed that two independent reviewers conducted quality assessment and a third reviewer conducted an independent quality check of the assessments
Were attempts to synthesise evidence appropriate?	No	See Section 3.6.3 (Methodological approach to the NMAs) and Appendix **Error! Reference source not found.**for a discussion of the company's methods and the ERG's critique of the syntheses of direct and indirect evidence

CASP=Critical Appraisals Skills Programme; CRD=Centre for Reviews and Dissemination
Source: LR*i*G in-house checklist

3.2 *ERG summary and critique of clinical effectiveness evidence*

3.2.1 Included trials

The company identified [redacted] studies ([redacted] records) that provided clinical effectiveness evidence of second- and later-line treatments for patients with pre-treated, advanced NSCLC. The ERG notes that:

- only the LIBRETTO-001 trial provided clinical effectiveness evidence of treatment with selpercatinib for patients with pre-treated, advanced *RET*+ NSCLC
- 12 of the identified studies included patients with *RET*+ NSCLC but were single-arm studies and therefore data from these studies could not be included in the company NMAs
- the company included 29 randomised controlled trials (RCTs) of adults with pre-treated, non-squamous NSCLC in at least one of their NMAs (see Section 3.6 of the ERG report and Appendix D.4.5 of the CS); however, none of these RCTs included patients with confirmed *RET*+ NSCLC.

3.2.2 Characteristics of the LIBRETTO-001 trial

The LIBRETTO-001 trial is an ongoing, multicentre, international, open-label, phase I/II basket trial that includes patients with tumour types other than NSCLC (medullary thyroid cancer, colon cancer and any solid tumour cancer). Phase I of the LIBRETTO-001 trial is a dose escalation phase that investigates the pharmacokinetics, safety and maximum tolerated dose of selpercatinib. Phase II of the trial is a dose expansion phase that investigates the efficacy and safety of the recommended phase II dose of selpercatinib (determined during phase I) for patients with *RET* fusion-positive tumours.

The LIBRETTO-001 trial is being conducted in 16 countries (United Kingdom, Canada, United States, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy and Israel). Clinical advice to the ERG is that the patient population and first-line treatment options across Canada and the European countries are likely to be consistent with clinical management in the UK NHS but first-line treatment options in the US may not always be comparable with care in the UK NHS. The relevance of first-line treatment options in the other countries in which the LIBRETTO-001 trial is being carried out is not known.

The key characteristics of phase II of the LIBRETTO-001 trial are summarised in Table 7.

Table 7 Key characteristics phase II of the LIBRETTO-001 trial

Trial parameter	Phase II of the LIBRETTO-001 trial
Design	• Ongoing, multicentre, international, open-label, phase I/II trial • 84 sites across 16 countries (United Kingdom, Canada, United States, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy and Israel) • Estimated completion date: May 2022
Patient population	• Patients (≥12 years) with 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 • Evidence of a *RET* gene alteration in the tumour • ECOG performance status ≤2 (≥16 years) or LPS ≥40% (<16 years) • No sudden deterioration 2 weeks prior to the first dose of selpercatinib
Treatment	• 160 mg BID oral selpercatinib
Primary outcome	• ORR based on RECIST v1.1 or RANO (dependent on tumour type), assessed by an IRC
Secondary outcomes	• BOR • DOR • Clinical benefit rate • CNS ORR • CNS DOR • PFS • OS • PK properties • Disease-related symptoms • Health-related quality of life
Safety outcomes	• AEs • Clinical safety laboratory values and vital signs
Report period for most recent interim analysis	• 9th May 2017 to 16th December 2019 • Interim analysis included data from patients who had enrolled by 17th June 2019, with a data cut-off date of 16th December 2019

AE=adverse event; BID=twice daily; BOR=best overall response; CBR=clinical benefit rate; CNS=central nervous system; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; HRQoL=health-related quality of life; IRC=independent review committee; LPS=Lansky Performance Score; ORR=objective response rate; OS=overall survival; PK=pharmacokinetic; PFS=progression-free survival; RANO=response assessment in neuro-oncology criteria; RECIST=response evaluation criteria in solid tumours; *RET*=rearranged during transfection
Source: Adapted from CS, Table 3 and Table 5

3.2.3 Characteristics of patients in the LIBRETTO-001 trial

The ERG notes that [redacted] patients were enrolled in the LIBRETTO-001 trial but only 329 patients had *RET*+ NSCLC. Phase II of the LIBRETTO-001 trial included 200 patients with pre-treated, advanced *RET*+ NSCLC who were receiving selpercatinib as a second- or later-line treatment and provided evidence relevant to the final scope[28] issued by NICE. Of the 200 patients, 184 patients had received prior treatment with platinum-based chemotherapy and were included in the IAS. Sixteen patients had received prior systemic therapy other than platinum-based chemotherapy (i.e., anti-PD-L1 or MKIs only) were included in supplementary analysis set 2 (SAS2). Definitions for each of the analysis sets described in the ERG report are presented in Table 8.

Table 8 LIBRETTO-001 trial phase II analysis sets for patients with pre-treated, advanced *RET*+ NSCLC

Analysis set	Analysis set description
Primary analysis set (PrAS) n=105	• Patients with confirmed *RET*+ NSCLC • Measurable disease by RECIST v1.1 by IA • Received ≥1 lines of prior platinum-based chemotherapy • Received at least one dose of selpercatinib • Patients who had enrolled by 17th June 2019
Integrated analysis set (IAS) n=184	• Includes all PrAS patients plus patients who satisfied the PrAS criteria but enrolled between 18th June 2019 and 16th December 2019.
Supplementary analysis set 2 (SAS2) n=16	• Patients with confirmed *RET*+ NSCLC • Measurable disease by RECIST v1.1 by IA • Received at least one dose of selpercatinib before the data cut-off (16th December 2019) • Received ≥1 prior systemic therapy **other than** platinum-based chemotherapy (i.e., anti-PD-L1 or MKIs only) • All other RET fusion positive NSCLC patients (for example, not part of the PrAS/IAS)

IA=Investigator Assessment; IAS=integrated analysis set; MKI=multi-kinase inhibitor: NSCLC=non-small cell lung cancer; PAS=primary analysis set; PD-L1=programmed death-ligand 1; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; *RET*=rearranged during transfection; SAS2=supplemental analysis set 2
Source: Adapted from CS, Table 6

[redacted] had received prior platinum-based chemotherapy and [redacted] had also received prior immunotherapy (Table 9). The ERG notes that some patients in the three analysis sets had received prior treatment with MKIs that are not listed as treatment options in the current NICE recommended treatment pathway.[5] This limits the generalisability of the results from the LIBRETTO-001 trial to NHS patients with pre-treated, advanced *RET*+ NSCLC.

Table 9 Prior treatments received by phase II LIBRETTO-001 trial patients with pre-treated, advanced *RET*+ NSCLC by analysis set

	PrAS (n=105)	**IAS (n=184)**	**SAS2 (n=16)**
Type of prior systemic therapy, n (%)			
Platinum chemotherapy	105 (100)	[redacted]	[redacted]
Anti-PD-L1 therapy	58 (55.2)	[redacted]	[redacted]
MKI	50 (47.6)	[redacted]	[redacted]
Number of prior systemic regimens, n (%)			
1-2	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]
Median	3.0 (1-15)	[redacted]	[redacted]
Prior radiotherapy, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Prior cancer-related surgery, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

IAS=integrated analysis set; MKI=multi-kinase inhibitor; PD-L1=programmed death-ligand 1; PrAS=primary analysis set; SAS2=supplementary analysis set 2 (prior other systemic therapy)
Source: Adapted from CS, Table 11

The baseline characteristics of patients participating in phase II of the LIBRETTO-001 trial, who provide clinical evidence relevant to the final scope[28] issued by NICE, are summarised in Table 10.

In the IAS, [redacted] of patients were female, [redacted] identified as white or Asian ethnicity, [redacted] had never smoked and [redacted] were in the 45 years to 64 years age group. The majority of patients in the IAS had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 at baseline [redacted] and had been diagnosed with Stage IV disease [redacted]

Most patient baseline characteristics were well balanced across the analysis sets. However, a higher proportion of patients who had received other systemic therapy only (anti-PD-L1 or MKIs only) (SAS2) presented with brain metastases at baseline [redacted] compared to patients who had received prior platinum chemotherapy [redacted]. Patients who had received other systemic therapy (anti-PD-L1 therapy or MKIs only) had a shorter median time from diagnosis to enrolment in the LIBRETTO-001 trial than patients who had received prior platinum chemotherapy [redacted].

Clinical advice to the ERG is that, compared to patients with pre-treated, advanced NSCLC seen in NHS practice, patients of Asian ethnicity and patients with a better ECOG PS (0 to 1) are over-represented in the LIBRETTO-001 trial.

Table 10 Characteristics of phase II LIBRETTO-001 trial patients with pre-treated, advanced *RET*+ NSCLC by analysis set

Baseline characteristic	PrAS (n=105)	IAS (n=184)	SAS2 (n=16)
Age, years			
Median (range)	61.0 (23-81)	[redacted]	[redacted]
Age group, n (%)			
12-17 years	[redacted]	[redacted]	[redacted]
18-44 years	[redacted]	[redacted]	[redacted]
45-64 years	[redacted]	[redacted]	[redacted]
65-74 years	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	62 (59.0)	[redacted]	[redacted]
Race, n (%)			
White	55 (52.4)	[redacted]	[redacted]
Black	5 (4.8)	[redacted]	[redacted]
Asian	40 (38.1)	[redacted]	[redacted]
Other	5 (4.8)	[redacted]	[redacted]
ECOG performance status, n (%)			
0	31 (29.5)	[redacted]	[redacted]
1	72 (68.6)	[redacted]	[redacted]
2	2 (1.9)	[redacted]	[redacted]
Disease stage at diagnosis, n (%)			
I-II	1 (1.0)	[redacted]	[redacted]
III	3 (2.9)	[redacted]	[redacted]
IV	101 (96.2)	[redacted]	[redacted]
Brain metastasis at baseline, n (%)			
Yes	38 (36.2)	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Cigarette smoking history, n (%)			
Never	75 (71.4)	[redacted]	[redacted]
Former	29 (27.6)	[redacted]	[redacted]
Current	1 (1.0)	[redacted]	[redacted]
Missing	0	[redacted]	[redacted]
Time from diagnosis, months			
Median (range)	[redacted]	[redacted]	[redacted]

ECOG=Eastern Cooperative Oncology Group; IAS=integrated analysis set (subset of prior platinum chemotherapy); PrAS=primary analysis set (prior platinum chemotherapy); SAS2=supplementary analysis set 2 (prior other systemic therapy)
Source: Adapted from CS, Table 9 and Table 10

3.2.4 Quality assessment of the LIBRETTO-001 trial

The company conducted a quality assessment of the LIBRETTO-001 trial using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies.[35] The responses to each quality item on the CASP[35] checklist are either, 'yes', 'no' or 'cannot tell'.

The sources of the company's information were three abstracts[37-39] and the entry for the LIBRETTO-001 trial recorded in ClinicalTrials.gov, an international database of clinical trials. The ERG assessment is based on information presented in the CS. The company's assessments and ERG comments are presented in Table 11. The ERG considers that the LIBRETTO-001 trial is of good methodological quality and that the data are well-reported. However, the ERG highlights that the LIBRETTO-001 trial is a single-arm trial and that, to date, only low numbers of OS and PFS events have occurred.

Table 11 Quality assessment of the LIBRETTO-001 trial

Quality assessment item	Company assessment	ERG assessment and comment
Did the study address a clearly focused issue?	Yes The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib (LOXO-292) in patients with advanced solid tumours including *RET* fusion-positive solid tumours, medullary thyroid cancer, and other tumours with *RET* activation. The primary endpoint is maximum tolerated dose and secondary endpoints include safety, ORR, and DOR	Yes
Was the cohort recruited in an acceptable way?	Cannot tell Abstract only but clear inclusion and exclusion criteria outlined on CT.gov. However, it is an open-label, single-arm study which could create selection bias	Yes The trial inclusion and exclusion criteria appear reasonable
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	Yes
Was the outcome accurately measured to minimise bias?	Yes Validated objective measurements were used. Tumour response was measured by a RECIST assessment and assessed by an IRC. Adverse events were not assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it is an open-label, single-arm study	Yes Adverse events were assessed using CTCAE (CS, Section B2.9.2, p118)
Have the authors identified all important confounding factors?	Cannot tell Abstract only	Yes Clinical advice to the ERG is that important confounding factors are performance status, burden of disease, brain metastases, stage of disease and

List the ones you think might be important, that the author missed.		number of metastases. These factors were considered in the company's pre-planned subgroup analyses
Have they taken account of the confounding factors in the design and/or analysis?	Cannot tell Abstract only	Yes See response to previous question
Was the follow up of subjects complete enough?	Cannot tell This is an ongoing trial	Yes No patients had been lost to follow-up at the time of the interim analysis reported in the CS
Was the follow up of subjects long enough?	Cannot tell This is an ongoing trial	No The trial is ongoing. The OS results reported in the CS are based on median follow-up times of [redacted] months (PrAS) and [redacted] months (IAS). Median OS was not reached. The PFS results are based on median follow-up times of 13.86 months (PrAS) and [redacted] months (IAS) The upper bounds of the OS and PFS CIs for the PrAS and IAS trial populations are reported as 'not estimable'
What are the results of this study?	LOXO-292 was well-tolerated and had marked antitumor activity in *RET*+ NSCLC patients, including those with resistance to prior MKIs and brain metastases from the initial results presented	Not clear The LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date
How precise are the results?	The results were precise. RECIST assessment was used on all scans to determine the ORR with an IRC. Adverse events will need to be assessed using CTCAE in the future	Not clear The LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date and the upper bounds of the OS and PFS CIs for the PrAS and IAS trial populations are reported as 'not estimable'
Do you believe the results?	Yes. However, the study is ongoing and abstract only	Not clear The LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date
Can the results be applied to the local population?	Yes. These results can be applied to NSCLC patients with *RET*-altered tumours	Yes However, it is difficult to confirm whether the patient population in the study is truly representative of all patients with *RET*+ NSCLC, given the low incidence[6] and patients with *RET*+ NSCLC are not routinely identified in the NHS
Do the results of this study fit with other available evidence?	Cannot tell. No targeted therapy is approved for patients with RET-altered tumours, but the results are similar to vandetanib which also selectively targets *RET* signalling	Not clear The LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date
What are the implications of this study for practice?	The results from this small single-arm study show LOXO-292 as a potential effective therapy for NSCLC patients with *RET*-altered tumours	Not clear The LIBRETTO-001 trial is an ongoing single-arm trial with few survival events to date

CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; DOR=duration of response; ERG=Evidence Review Group; IAS=integrated analysis set; IRC=independent review committee; LOXO-292=selpercatinib; NA=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PrAS=primary analysis set; RECIST= Response Evaluation Criteria in Solid Tumours
Source: Adapted from CS, Table 13

3.2.5 Statistical approach adopted for the analysis of the LIBRETTO-001 trial data

Information relevant to the statistical approach taken by the company has been extracted from the CS, the most recent versions of the trial protocol (version 8.0, dated 10 May 2019) and the trial statistical analysis plan (TSAP, version 1.0, dated 8 August 2019), available as supplementary documents to the journal publication of the LIBRETTO-001 trial.[40] A summary of the ERG checks of the pre-planned statistical approach used by the company to analyse data from the LIBRETTO-001 trial is provided in Table 12.

Table 12 ERG assessment of statistical approaches used in the LIBRETTO-001 trial

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations of phase II of the LIBRETTO-001 trial are clearly defined in Table 6 of the CS and pre-specified (TSAP, Section 5) Clinical effectiveness results are presented in the CS (Section B.2.5.2) for two pre-treated populations (the primary analysis set [PrAS] and the integrated analysis set [IAS])
Was an appropriate sample size calculation pre-specified?	Yes	Sample size and design considerations of phase I and phase II of the LIBRETTO-001 trial are outlined in Table 7 of the CS and the pre-specified Protocol (Section 8.3). Additional calculations of the sample size within the PrAS were also pre-specified (TSAP, Section 4) The ERG is satisfied that designs and sample sizes are appropriate for the dose escalations and dose expansion objectives of phase I and phase II, respectively, of the LIBRETTO-001 trial
Were all protocol amendments made prior to analysis?	Yes	A summary of changes from version 1.0 to version 8.0 (the latest version, 10th May 2019) of the LIBRETTO-001 trial protocol are provided as a supplementary document to the publication of the LIBRETTO-001 trial[40] Amendment 5 (30 May 2018) was the largest amendment. It was issued to update the trial design from a phase I study to phase I/II study. Other amendments mainly relate to minor clarification of inclusion criteria, phase I and phase II study design, outcome definitions and data collection procedures The ERG considers that all protocol amendments are appropriate and notes that all were made prior to the latest data cut-off date (16th December 2019)
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary outcome of phase II of the LIBRETTO-001 trial is ORR (CS, Table 8) which was pre-defined (TSAP, Section 3.1). Secondary efficacy outcomes of phase II of the LIBRETTO-001 trial are DoR, PFS and OS (CS, Table 8), which were pre-defined (TSAP, Sections 10.5, 10.7 and 10.8 respectively) Appropriate statistical analysis methods for the primary and secondary efficacy outcomes were described in the CS (Table 7, Table 8) and were pre-specified (TSAP, Sections 10.2, 10.5, 10.7 and 10.8)
Was the analysis approach for PROs appropriate and pre-specified?	Not pre-specified Partly appropriate	An exploratory endpoint of phase II of the LIBRETTO-001 trial was predefined as change from baseline in disease-related symptoms and HRQoL as measured by EORTC QLQ-C30 (Protocol, Section 8.1). The analysis approach is described in the CS (Table 8; Section B.2.5.3). The analysis population is defined as the “QLQ-C30 Analysis Set” (i.e., patients with *RET*+ NSCLC who had completed an EORTC QLQ-C30 baseline assessment) The ERG considers that the descriptive analysis approach was appropriate but notes that neither the analysis population nor the analysis approach were pre-defined in the trial protocol or TSAP
Was the	Yes	AEs were assessed and graded using the CTCAE version 4.03 classification

analysis approach for AEs appropriate and pre-specified?		system within the SES (CS, Section B2.9.2, p118). AEs were estimated as numbers and percentages of patients experiencing events; no formal statistical analyses of AEs were conducted. Summaries of TEAEs occurring in ≥15% of patients, Grade 3-4 AEs occurring in ≥2% of patients and AEs of special interest, AEs leading to treatment discontinuation, SAEs and death are presented in the CS (Section B.2.9 pp118-123) The ERG is satisfied that the approach employed was pre-defined (Protocol, Section 9) and is appropriate
Was a suitable approach employed for handling missing data?	Yes	No imputation of missing data is conducted within the LIBRETTO-001 trial, except for imputation of partial dates (TSAP, Section 7.1). Time-to-event outcomes (DoR, PFS, OS) are censored at the last available efficacy evaluation for patients missing two or more consecutive study visits (TSAP, Section 10.5) The ERG agrees that it is appropriate not to conduct any data imputation and to present data as recorded
Were all subgroup analyses pre-specified?	Yes	Subgroup analyses for the primary outcome (ORR) in the PrAS were prespecified (TSAP, Section 10.0) by demographic variables (age, sex, race, ECOG PS, metastatic disease, investigator assessed CNS metastases at baseline), by type of *RET* fusion partner and type of *RET* molecular assay used and by the number of previous therapies and types of previous therapies used (CS, Table 5). Results of these pre-specified subgroup analyses are presented in the CS (Table 23, Table 24, Table 25). Subgroup analyses were not performed in the IAS

AE=adverse event; CNS=central nervous system; CTCAE=common terminology criteria for adverse events; DoR=duration of response; 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; IAS=integrated analysis set; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PrAS=primary analysis set; PRO=patient reported outcome; *RET*=rearranged during transfection; SAE=serious adverse event; SAS1=supplemental analysis set 1; SES=safety analysis set; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan
Source: Extracted from the CS, the protocol and statistical analysis plan of the LIBRETTO-001 trial, available as supplementary documents to the publication of the LIBRETTO-001 trial,[40] the company's response to the clarification letter and ERG comment

3.3 *Efficacy results from the LIBRETTO-001 trial*

All results presented in this section relate to patients with pre-treated, advanced *RET*+ NSCLC participating in phase II of the LIBRETTO-001 trial (PrAS and IAS datasets only).

Efficacy results presented in the CS are from a pre-planned interim analysis (data cut-off date of 16th December 2019) including patients enrolled in the LIBRETTO-001 trial by 17th June 2019. A summary of key efficacy results for the PrAS (n=105) and IAS (n=184) is presented in this section.

At the time of the interim analysis, [redacted] and [redacted] of patients in the PrAS and IAS respectively were still receiving selpercatinib. The most common reason for treatment discontinuation was [redacted] (CS, Table 12)

3.3.1 Overall survival

A summary of OS results for the PrAS and IAS is provided in Table 13.

Table 13 Summary of LIBRETTO-001 trial OS results: PrAS and IAS (pre-treated)

	PrAS (n=105)	IAS (n=184)
Median follow-up (25, 75 percentiles), months	[redacted]	[redacted]
Died: n (%)	[redacted]	[redacted]
Alive: n (%)	[redacted]	[redacted]
Median OS (95% CI), months	[redacted]	[redacted]

CI=confidence interval; IAS=integrated analysis set; NE=not evaluable; OS=overall survival; PrAS=primary analysis set;
Source: Extracted and adapted from the CS, Table 21

At the time of the interim analysis, the median follow-up was [redacted] months and [redacted] months and [redacted] patients and [redacted]) patients had died in the PrAS and IAS, respectively. As less than 50% of patients had died at the time of analysis, median OS had not been reached in either the PrAS or the IAS.

3.3.2 Progression-free survival

A summary of PFS results (by independent review committee assessment [IRC]) for the PrAS and IAS is provided in Table 14. Results by investigator assessment are very similar to IRC assessment (CS, Appendix L, Table 71 and Table 74).

Table 14 Summary of LIBRETTO-001 trial PFS (IRC) results: PrAS and IAS (pre-treated)

	PrAS (n=105)	IAS (n=184)
Median follow-up (25, 75 percentiles), months	13.86 [redacted]	[redacted]
Disease progression: n (%)[a]	[redacted]	[redacted]
Died (without disease progression): n (%)[a]	[redacted]	[redacted]
Censored: n (%)	61 (58.1)	[redacted]
Alive without disease progression: n (%)[a]	[redacted]	[redacted]
Median PFS (95% CI), months	16.53 (13.7 to NE)	[redacted]

[a] Disease progression assessed by IRC
CI=confidence interval; IAS=integrated analysis set; IRC=independent review committee; NE=not evaluable; PFS=progression free survival; PrAS=primary analysis set
Source: Extracted and adapted from the CS, Table 20

At the time of the interim analysis, the median follow-up was 13.86 months and [redacted] months and [redacted] patients and [redacted]) patients were alive without disease progression (by IRC assessment) in the PrAS and IAS, respectively. In the PrAS, the median PFS (95% confidence interval [CI]) was 16.53 (13.7 to NE) months and in the IAS it was [redacted] months. The company notes that, at the time of the latest data-cut off, PFS data were immature (CS, Section B.2.12, p125).

3.3.3 Overall response rate and duration of response

A summary of ORR and DoR results (by IRC assessment) for the PrAS and IAS pre-treated populations are provided in Table 15. Results by investigator assessment of response are very similar to IRC assessment (CS, Appendix L, Table 68, Table 70, Table 72 and Table 73).

Table 15 Summary of LIBRETTO-001 trial BOR, ORR and DoR (IRC) results: PrAS and IAS (pre-treated)

Best overall response[a]	PrAS (n=105)	IAS (n=184)
Overall response: n (%)	67 (63.8)	[redacted]
Complete response: n (%)	2 (1.9)	[redacted]
Partial response: n (%)	65 (61.9)	[redacted]
Stable disease: n (%)	30 (28.6)	[redacted]
Progressive disease: n (%)	4 (3.8)	[redacted]
Not evaluable: n (%)[c]	4 (3.8)	[redacted]
ORR (95% CI)	[redacted]	[redacted]
Median DoR (95% CI), months	17.51 (12.0 to NE)	[redacted]

[a] Response assessed by IRC
CI=confidence interval; DoR=duration of response; IAS=integrated analysis set; IRC=independent review committee; NE=not evaluable; ORR=overall response rate; PrAS=primary analysis set
Source: Extracted and adapted from the CS, Table 18 and Table 19

In the PrAS, the ORR was [redacted]) and in the IAS, the ORR was [redacted]). The majority of responses were partial responses; only two patients (1.9%) in the PrAS and [redacted] in the IAS achieved a complete response. The median DoR was [redacted].

Subgroup analyses of ORR and DoR in the PrAS by demographic variables (age, sex, race, ECOG PS, metastatic disease, investigator assessed CNS metastases at baseline), type of *RET* fusion partner, type of *RET* molecular assay used, number of previous therapies and type of previous therapies used are presented in the CS (Table 23, Table 24 and Table 25). ORR across subgroups was consistent with ORR in the PrAS, ranging from [redacted] up to [redacted] (in patients with other *RET* fusion partner and with CCDC6 *RET* fusion partner respectively). The ERG notes that small sample sizes of the subgroups, particularly for types of *RET* fusion partner and type of *RET* molecular assay used, should be considered when drawing conclusions from subgroup results.

3.4 *Patient reported outcomes from the LIBRETTO-001 trial*

HRQoL data for patients with pre-treated, advanced *RET*+ NSCLC were provided in Section B.2.5.3 of the CS. The company confirmed, in response to clarification question A3, that the 184 patients discussed in Section B.2.5.3 of the CS are the same patients as in the IAS population. To be included in the analysis, patients were required to provide a baseline assessment score (CS, p85).

HRQoL data were collected during the LIBRETTO-001 trial using the European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30 (EORTC QLQ-C30).[41] HRQoL was assessed at baseline and every 8 weeks thereafter until the end of treatment visit.

The EORTC QLQ-C30 questionnaire[41] is cancer-specific and consists of five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a HRQoL scale, a financial impact scale and five physical symptom scales. The LIBRETTO-001 trial HRQoL data were not used to inform the company cost effectiveness analysis.

The company considered, in line with assumptions made in oncology literature,[42] that a 10-point difference from baseline assessment score for a QLQ-C30 domain was a clinically meaningful difference. The company defined a clinically meaningful improvement in mean QLQ-C30 domain score as an increase of ≥10-points from baseline score and a clinical meaningful worsening as a decrease of ≥10-points from their baseline score.

3.4.1 Summary of EORTC QLQ-C30 and QLQ-LC13 data

A summary of HRQoL results for the IAS population is provided in Table 16.

The mean baseline score for global health status/quality of life (QoL) subscale was [redacted] (standard deviation [SD]: [redacted]). The company reported that [redacted] ([redacted]) patients experienced a clinically meaningful improvement in the global health status/QoL subscale score with a median time to definite improvement of [redacted] months (Table 16). The company did not report the proportion of patients who experienced a clinically meaningful worsening in the global health status/QoL subscale score.

The average scores for the five functional scales were each [redacted] points at baseline. The proportions of patients with any clinically meaningful improvement or worsening from baseline score for the five functional scales are presented in Table 16. The company reported that there were no consistent clinically meaningful differences in mean patient scores for the five functional scales.

Across most of the EORTC QLQ-C30 subscales, a numerically higher proportion of patients reported improved rather than worsened scores compared to baseline (Table 16). The company reported that the EORTC QLQ-C30 subscales scores showed that, compared with baseline scores, most pre-treated, advanced *RET*+ NSCLC patients had stable or improved HRQoL following treatment with selpercatinib.

Table 16 EORTC-QLQ-C30: proportions of patients whose HRQoL improved or worsened from baseline

EORTC QLQ-C30 subscale	IAS (n=184)		
	Baseline score, mean (SD)	Improved n (%)	Worsened n (%)
Global health status/QoL	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30; IAS=integrated analysis set; QoL=quality of life; NR=not reported; SD=standard deviation
Source: Extracted from CS, p85

3.5 Safety and tolerability results from the LIBRETT0-001 trial

Safety and tolerability data from the LIBRETTO-001 trial are presented in the CS (Section B.2.9). The AEs arising during the trial were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.[43] The AE results presented in the CS are from the 16th December 2019 data cut.

The safety and tolerability of selpercatinib was assessed in all patients enrolled in the LIBRETTO-001 trial (regardless of tumour type or treatment history) and specifically in those patients with *RET*+ NSCLC. The safety data discussed in this section of the ERG report are from the 329 patients with *RET*+ NSCLC included in the NSCLC Safety Analysis Set (NSCLC SAS) of the LIBRETTO-001 trial. The NSCLC SAS incorporates five categories of patients who were treated with selpercatinib:

- patients with pre-treated disease who had received prior platinum-based chemotherapy (n=184)
- patients with pre-treated disease who had received prior systemic therapy other than platinum-based chemotherapy (n=16)
- patients with untreated disease (n=39)
- patients with non-measurable disease (n=14)
- patients treated between June 2019 and December 2019 and who were outside the data cut-off date for inclusion in the pre-planned interim analysis (n=76).

<u>Summary of LIBRETTO-001 trial adverse events</u>

The range of starting doses and average treatment duration are provided in the CS (Table 38). Over [redacted] of patients in the NSCLC SAS received a starting dose (the anticipated licensed dose) of 160mg selpercatinib BID. The mean treatment duration was [redacted] months (range: [redacted] months) and the mean relative dose intensity (RDI) was [redacted] (CS, Table 39). Details of dose modifications are presented in Table 40 of the CS. Dose reductions due to AEs were implemented in [redacted] of patients, and [redacted] of patients had their dose interrupted due to AEs. A few ([redacted]) patients discontinued treatment permanently because of a treatment emergent AE (TEAEs) and [redacted] of patients had their dose of selpercatinib increased.

A summary of the AEs reported during the LIBRETTO-001 trial is presented in Table 17. None of the [redacted] reported within 28 days of the last dose of selpercatinib were attributed to treatment.

Table 17 Summary of LIBRETTO-001 trial adverse event data

Type of AE	NSCLC SAS (n=329)	
	Treatment-related AEs n (%)	All AEs n (%)
Any AE	[redacted]	[redacted]
Grade 3 or 4 AE	[redacted]	[redacted]
AE leading to treatment discontinuation	[redacted]	[redacted]
SAE	[redacted]	[redacted]
Fatal AE	[redacted]	[redacted]

AE=adverse event; NSCLC=non-small cell lung cancer; SAE=serious adverse event; NSCLC SAS=non-small cell lung cancer safety analysis set
Source: Adapted from CS, Table 41

Treatment-emergent adverse events

The frequencies of common TEAEs of all grades (≥15% in any of the safety analysis sets) are presented in Table 42 of the CS. Nearly all [redacted]) patients in the NSCLC SAS experienced TEAEs and these were classified as mainly Grade 1 or Grade 2 events. The company considers (CS, p119) that these Grade 1 and Grade 2 events would be manageable in clinical practice.

The most common TEAEs were dry mouth ([redacted]), diarrhoea ([redacted]), aspartate aminotransferase (AST) increase ([redacted]), hypertension ([redacted]), alanine transaminase (ALT) increase ([redacted]), peripheral oedema ([redacted]), fatigue ([redacted]), nausea ([redacted]) and constipation ([redacted]).

Grade 3 and Grade 4 treatment-emergent adverse events

The Grade 3 and Grade 4 TEAEs reported in ≥2% of patients in the LIBRETTO-001 trial are presented in Table 18. Almost [redacted]) of the Grade 3 or Grade 4 TEAEs were considered by trial investigators as being related to treatment with selpercatinib.

Table 18 Grade 3 to Grade 4 adverse events in ≥2% of patients

Type of AE	NSCLC SAS (n=329)	
	TEAEs considered as related to treatment n (%)	All events, regardless of attribution n (%)
≥1 Grade 3–4 AEs	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]
ECG QT prolonged	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; NSCLC SAS=non-small cell lung cancer safety analysis set; NR=not reported; TEAE=treatment emergent adverse event
Source: Adapted from CS, Table 43

Adverse events of special interest

The company considered that increased liver enzymes (ALT/AST), drug hypersensitivity, hypertension and QT prolongation were AEs of special interest (AEOSI). The company highlighted (CS, p121) that these events were generally easy to monitor and were reversible by dose modification. The only AEOSI reported by the company that affected patients in the NSCLC SAS was hypertension; this occurred in [redacted] of patients as an any Grade event and in [redacted] of patients as a Grade 3 to 4 event.

Summary of safety results

The company states that selpercatinib was well-tolerated and that only a small proportion of patients discontinued treatment due to treatment-related [redacted] or treatment-emergent [redacted] AEs. Overall, the AEs experienced by patients in the LIBRETTO-001 trial were mostly Grade 1 or 2 and were largely manageable and reversible (with dose interruption, dose reduction, or concomitant medication). Clinical advice to the ERG is that selpercatinib seems to have a manageable toxicity profile. The ERG highlights that as the source of the safety data is a phase II single-arm trial, the relative safety of selpercatinib versus comparator treatments cannot be determined.

3.6 *ERG critique of the indirect evidence*

In the absence of a head-to-head comparison of the efficacy of selpercatinib versus comparator treatments relevant to the final scope[28] issued by NICE, the company performed NMAs of ORR, OS and PFS.

3.6.1 Critique of trials included in the NMAs

The company conducted a systematic literature review (see Section 3.1 of this report for further details). The company search process identified 29 relevant RCTs of comparator treatments in populations of adults with non-squamous, pre-treated NSCLC that could be included in at least one of the company's NMAs; a list of these studies can be found in the CS (Appendix D.4.5; Table 36). In total, including the LIBRETTO-001 trial, 30 trials were eligible for inclusion in at least one of the company's NMAs.

A summary of the characteristics of the trials included in the NMAs is provided in Appendix 9.1 to this ERG report. The ERG considers that the trial design characteristics were similar across trials. All were phase II or phase III trials and the majority of these (22 out of 30, 73%) were open-label trials. However, where reported, the median duration of follow-up ranged from 7.1 months[44] to 60.6 months.[45]

Eight trials of comparator treatments recruited patients with non-squamous NSCLC only.[46-53] For the remaining trials of comparators, subgroup results were included in the NMAs; non-squamous NSCLC subgroup (13 trials[45,54-65]), adenocarcinoma subgroup (6 trials[44,66-70]), EGFR-negative mutation subgroup (1 trial[71]) and EGFR wild type mutation subgroup (1 trial[72]).

Patient baseline characteristics (age, gender, race, smoking status, ECOG, CNS metastases, EGFR mutation, Kirsten rat sarcoma (KRAS) mutation, history of metastatic disease, PD-L1 expression level, stage at baseline/initial diagnosis, time since initial diagnosis, prior lines of therapy [number of lines and type of therapy], time since prior therapy) were summarised in an Excel spreadsheet provided as part of the reference pack that accompanied the CS (Reference Pack, Second Line systematic literature review [SLR] documents).

The ERG considers that the baseline characteristics of the patients participating in the trials included in the company NMAs (including the LIBRETTO-001 trial) are generally similar and it is unlikely that any minor differences in patient baseline characteristics have an important impact on NMA results. The ERG considers that the greatest source of trial-related uncertainty is that the LIBRETTO-001 trial data that informed the company NMAs were from a *RET*+ NSCLC population, whilst the other 29 trials provided data from a wider NSCLC population and it is unknown how many patients within those trials had *RET*+ NSCLC.

3.6.2 Quality assessment of the trials included in the NMAs

The company conducted a quality assessment using a seven question checklist based on the recommendations of the Centre for Reviews and Dissemination,[73] according to the minimum criteria set out in the NICE Guide to the Methods of Technology Appraisal[74] for all trials included in the NMAs (CS, Reference Pack, Second Line SLR documents).

Overall, the ERG agrees with the quality assessments made by the company and notes that the majority of trials of comparators were generally of good quality with adequate methods of randomisation and allocation concealment, balanced patient characteristics and prognostic factors at baseline, appropriate use of an intention-to-treat analysis and reporting of all measured outcomes. However, the majority of the trials (22 out of 30, 73%) were of an open-label design and were therefore at risk of detection and performance biases. The ERG is not concerned that any detection and performance biases present within the trials due to lack of blinding would have had an important impact on NMA results.

3.6.3 Methodological approach to the NMAs

Full details of the ERG summary and critique of the company approach to the NMAs is provided in Appendix 9.2 to this ERG report. In summary, for the OS and PFS NMAs, to connect the selpercatinib arm of the LIBRETTO-001 trial to the networks, the company generated OS and PFS pseudo-control (reference) arms. These arms were created using data from 451 patients with non-squamous NSCLC who had received docetaxel+placebo in the REVEL RCT;[58] the ERG highlights that the first-line treatment received by patients in this trial was PDC. The REVEL trial[58] data were adjusted to reflect *RET*+ status using data from [redacted] patients (*RET+:* n=[redacted]; *RET-:* n=[redacted]) from the Flatiron database[75] (CS, Appendix D, Section D.1.7). Using the pseudo-control (reference) arms and data from the patients in the IAS of the LIBRETTO-001 trial, the company estimated treatment effects (HRs and 95% CIs) for OS and PFS for the comparison of selpercatinib and pseudo-control (reference) arm data. The ORR NMA used raw (unadjusted) data from the docetaxel+placebo control arm of the REVEL trial[58] and selpercatinib data from the LIBRETTO-001 trial.

The company connected the selpercatinib data from the LIBRETTO-001 trial to the OS and PFS networks to allow indirect comparisons with relevant comparators which were "reflective of *RET*+ status" (CS, Appendix D.1.7). The ERG agrees with the company that the process of generating pseudo-control arms is associated with inherent uncertainty (CS, Section B2.8.3). Due to uncertainties relating to the complexity of the two stage company approach to generating the pseudo-control (reference) arms; a multivariable adjustment analysis and an additional targeted minimum loss-based estimation (TMLE) adjustment analysis, as well as concerns highlighted by the company (CS, Section B2.8.3) that treatment effect may have been overestimated in these pseudo control (reference) arms, the ERG does not consider that the estimated HRs and 95% CIs for selpercatinib versus the pseudo-control (reference) arms used within the OS and PFS NMAs are robust.

Additional areas of concern relating to the NMAs are:

- the inclusion of data from comparators in the NMAs which are not relevant to the decision problem introduces uncertainty into the NMA results (Appendix 9.2)
- the ORR NMA used raw (unadjusted) data from the docetaxel+placebo control arm of the REVEL trial[58] and selpercatinib data from the LIBRETTO-001 trial; this approach introduces uncertainty into the ORR NMA results
- the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a *RET*+ NSCLC population, nor have these networks been adjusted for any prognostic factors associated with *RET*+ NSCLC
- differences in the definition of PFS between the REVEL trial,[58] the LIBRETTO-001 trial, and the Flatiron database are likely to have introduced uncertainty into the generation of the PFS pseudo-control arm, and therefore into the PFS NMA results
- there was evidence of violation of the assumption of proportion hazards (PH) for three trials in the PFS NMA[46,51,58] and for two trials in the OS NMA.[46,51] Additional analyses using a fractional polynomial approach were conducted by the company for the PFS NMA. Using a fractional polynomial approach was deemed inappropriate by the company for OS due to the immaturity of the LIBRETTO-001 trial OS data. The impact of PH violation on the results of the OS NMA is not known.

3.6.4 Results from the NMAs

Table 19 provides a summary of the number of trials and patients contributing to the NMAs, and the locations of the network diagrams for each outcome. References for the trials contributing to the NMA for each outcome can be found in the CS (Table 36, Appendix D.4.5).

Table 19 Summary of numbers of trials and patients contributing to NMAs

Outcome	Number of trials: n (%)	Number of patients with non-squamous NSCLC[a,b]	Network diagrams
ORR	18 (60%)	5,683	CS, Figure 26
PFS	27 (90%)	9,148	CS, Figure 28
OS	25 (83%)	10,261	CS, Figure 30

[a] Including 184 patients who received selpercatinib from the LIBRETTO-001 trial IAS and 451 patients used to generate the pseudo-control arm to connect selpercatinib to the networks
[b] Results included data from trials recruiting patients with non-squamous NSCLC only (n=8), subgroup results for non-squamous NSCLC (n=13), subgroup results for adenocarcinoma (n=6), subgroup results for EGFR-negative mutation (n=1) and EGFR wildtype mutation (n=1)
EGFR=epidermal growth factor receptor; IAS=integrated analysis set; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; PFS=progression-free survival; ORR=overall response rate; OS=overall survival
Source: Extracted and adapted from CS, Reference pack, Second Line SLR documents

Results from the company fixed-effects NMAs for OS, PFS and ORR for relevant comparators versus docetaxel+placebo (i.e., the pseudo-control arm) and for relevant comparators versus selpercatinib are provided in Table 20.

Table 20 Company NMA results for selpercatinib and comparators

Second-line population	Comparator	ORR[a] OR (95% CrI)	PFS[b] HR (95% CrI)	OS[b] HR (95% CrI)
Comparator versus docetaxel+placebo[c]				
All non-squamous NSCLC	Selpercatinib	[redacted]	[redacted]	[redacted]
	Atezolizumab	No data available[e]	No data available[e]	[redacted]
	Nintedanib+docetaxel	[redacted]	[redacted]	[redacted]
Non-squamous NSCLC and PD-L1≥1%	Nivolumab	[redacted]	[redacted]	[redacted]
	Pembrolizumab	No data available[e]	[redacted]	[redacted]
Selpercatinib versus comparator[d]				
All non-squamous NSCLC	Docetaxel+placebo	[redacted]	[redacted]	[redacted]
	Atezolizumab	No data available[e]	No data available[e]	[redacted]
	Nintedanib+docetaxel	[redacted]	[redacted]	[redacted]
Non-squamous NSCLC and PD-L1≥1%	Nivolumab	[redacted]	[redacted]	[redacted]
	Pembrolizumab	No data available[e]	[redacted]	[redacted]

[a] ORR results for selpercatinib versus comparators were estimated from a fixed-effects hierarchical exchangeable NMA model adjusted for the proportion of Asian patients. ORR results for comparators vs docetaxel+placebo were estimated from an unadjusted fixed-effects NMA model.
[b] OS and PFS results were estimated from a fixed-effects hierarchical exchangeable NMA model adjusted for age
[c] OR >1 and HRs<1 indicate an advantage to the comparator over docetaxel+placebo. Green highlighted cells represent statistically significant results in favour of the comparator over docetaxel+placebo
[d] OR>1 and HRs<1 indicate an advantage to selpercatinib over the comparator. Green highlighted cells represent statistically significant results in favour of selpercatinib over the comparator
[e] ORR data were not available for atezolizumab or pembrolizumab and PFS data were not available for atezolizumab
CrI=credible Interval; HR=hazard ratio; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1; PFS=progression-free survival; OR=odds ratio; ORR=overall response rate; OS=overall survival
Source: CS, extracted and adapted from Table 35, Table 36 and Table 37; and company response to question A19 of the clarification letter

A statistically significant advantage for selpercatinib over the docetaxel+placebo pseudo-control arm was reported for all outcomes. Furthermore, a statistically significant advantage was reported for selpercatinib over nintedanib+docetaxel for all outcomes and over both nivolumab and pembrolizumab for PFS (PD-L1 ≥1% subgroup).

The ERG also notes that the company's NMA results show no statistically significant difference between nintedanib+docetaxel and docetaxel+placebo for any outcome. This is contrary to results from the LUME-Lung 1 trial[70] of nintedanib+docetaxel versus docetaxel+placebo which are included within the NMAs. The LUME-Lung 1 trial[70] showed a statistically significant advantage for nintedanib+docetaxel over docetaxel+placebo for both PFS (HR 0.77, 95% CI: 0.62 to 0.96) and OS (HR 0.83, 95% CI: 0.70 to 0.99) and nintedanib+docetaxel is recommended by NICE[25] for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy. The inconsistency between the NMAs and the LUME-Lung 1 trial[70] results may reflect the influence of the additional evidence in the networks, including evidence from comparators that the company had deemed irrelevant. Alternatively, the lack of a statistically significant difference between nintedanib+docetaxel and docetaxel+placebo in the NMAs, contrary to the results of the LUME-Lung 1 trial[70] may be due to the company concerns that the relative treatment effect within the docetaxel+placebo pseudo-control arm has been overestimated.

3.6.5 Company indirect comparisons: ERG conclusions

The results of the company NMAs showed a statistically significant advantage for selpercatinib over the docetaxel+placebo pseudo-control (reference) arm and over nintedanib+docetaxel for OS and PFS, and over nivolumab and pembrolizumab for PFS (PD-L1 ≥1% subgroup).

The ERG emphasises that due to the inherent uncertainties associated with data inputs and the generation of the docetaxel+placebo pseudo-control (reference) arms in the OS and PFS NMAs, the results are not robust and should not be used for decision making. The ERG considers that definitive conclusions regarding the direction and magnitude of the relative effect of selpercatinib over comparators cannot be drawn.

3.7 *Clinical summary and key issues identified by the ERG*

3.7.1 Summary

The company has limited the focus of this appraisal to patients with pre-treated, advanced non-squamous *RET*+ NSCLC.

The company has provided evidence to demonstrate the effectiveness of selpercatinib from phase II of the LIBRETTO-001 trial; this is an ongoing, multicentre, international, open-label, phase I/II basket trial. The company considers that the relevant comparators to selpercatinib are pembrolizumab, nivolumab, atezolizumab, and nintedanib+docetaxel. Comparator effectiveness evidence has been provided by the company in the form of NMA results.

Results from the LIBRETTO-001 trial showed that selpercatinib was well-tolerated; only a small proportion of patients discontinued treatment due to treatment-related ([redacted]) or treatment-emergent ([redacted]) AEs. Most AEs experienced by patients in the LIBRETTO-001 trial were Grade 1 or 2 and were largely manageable and reversible (with dose interruption, dose reduction, or concomitant medication).

Clinical advice to the ERG is that patients with NSCLC in the NHS are not routinely tested for *RET* fusion status and a national NHS Genomic Medicine Service to provide Next Generation Sequencing has yet to be established.

3.7.2 Key issues identified by the ERG

Clinical advice to the ERG is that limiting the focus of this appraisal to patients with pre-treated, advanced non-squamous *RET*+ NSCLC was appropriate.

The LIBRETTO-001 trial is well-designed and well-reported and is of good methodological quality. However, the LIBRETTO-001 trial is a single-arm trial and this, combined with the number of events reported in the IAS dataset (OS: [redacted] [[redacted]]; PFS: [redacted] [[redacted]) and median follow up times (OS: [redacted] months; PFS: [redacted] months) mean that the relative and absolute effectiveness of selpercatinib are currently unknown.

The generalisability of LIBRETTO-001 trial results to patients treated in the NHS is unclear as *RET*+ NSCLC is an uncommon type of NSCLC (estimated to affect between 1% and 2% of the NSCLC population)[6] that is not routinely tested for in the NHS. The company appears to be positioning selpercatinib as a second-line treatment (see economic analysis). The ERG considers that the clinical effectiveness evidence presented in the CS is insufficient to demonstrate the clinical effectiveness of selpercatinib in the second-line setting as a treatment for *RET*+ NSCLC.

In contrast to the company, the ERG considers that the only relevant comparators are nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC; clinical advice to the ERG is that nearly all patients with advanced non-squamous *RET*+ NSCLC who are suitable for treatment will receive immunotherapy in the first-line setting and, therefore, will not receive another immunotherapy as a second-line treatment.

The only evidence presented by the company to demonstrate the relative effectiveness of selpercatinib versus all comparators has been generated by the company NMAs. However, the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a confirmed *RET*+ NSCLC population, nor have the networks been adjusted for any prognostic factors associated with *RET*+ NSCLC. In addition, the ERG has concerns about the generation of the pseudo-control (reference) arms used in the company NMAs. In light of the data input and methodological concerns, the ERG considers that definitive conclusions regarding the direction and magnitude of the relative effect of selpercatinib versus the comparators cannot be made from the company OS and PFS NMAs.

4 COST EFFECTIVENESS EVIDENCE

The CS provides cost effectiveness evidence to support the use of selpercatinib to treat adults with advanced non-squamous *RET*+ NSCLC in the first- and later line settings. However, on 22nd October 2020, the company made the decision to restrict the scope of this appraisal to pre-treated patients.

The three key components of the economic evidence presented in the CS are (i) a systematic review to identify data to inform economic modelling decisions, (ii) a systematic review to identify utility and cost data, and (iii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 *ERG critique of the company systematic review methods of review(s)*

As selpercatinib is a first in class therapy for adults with advanced *RET*+ NSCLC there are no published cost effectiveness studies for a selective RET kinase inhibitor in this population.

The company searched for utility/HRQoL, resource use and cost data needed to inform modelling decisions. Recent relevant NICE NSCLC Technology Appraisals were used to identify data that had been accepted by NICE as the best available at the time of each identified appraisal. A search was undertaken to identify published NSCLC and thyroid cancer data published from 1 January 2015 to 12 August 2019 (the date the searches were carried out). Details of the strategies used by the company to identify utility/HRQoL, resource use and cost data for second-line NCSLC treatments are provided in the CS (Appendix H). A summary of studies reporting utilities is also provided in Appendix H (Table 52) and a summary of the studies reporting resource use or cost data is provided in Appendix I (Table 53).

An assessment of the extent to which the company's review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 21.

Table 21 ERG appraisal of company review methods

Review process*	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	NA
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	NA
Was the quality assessment conducted by two or more reviewers independently?	NA
Were attempts to synthesise evidence appropriate?	NA

* The search strategy also identified thyroid cancer publications
ERG=Evidence Review Group; NA=not applicable
Source: LR*i*G in-house checklist

4.2 *ERG conclusions regarding company systematic review methods of review(s)*

Searches carried out by the ERG did not identify any relevant studies. The ERG has no concerns about the methods used by the company to identify evidence to inform modelling decisions. Overall, the ERG is satisfied that there are no relevant economic studies of selpercatinib or other advanced *RET*+ NSCLC treatments.

4.3 *ERG summary and critique of the company's submitted economic evaluation*

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 22 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on the company's economic evaluation
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. Utility values from NICE TA484[26] were used
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

ERG=Evidence Review Group; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[76] and ERG comment

Table 23 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	No	Evidence for selpercatinib has been drawn from the immature, single-arm, phase II LIBRETTO-001 trial. The ERG considers that the intervention and comparator survival evidence used by the company is unreliable
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG=Evidence Review Group; NMA=network meta-analysis
Source: Drummond and Jefferson 1996[77] and ERG comment

4.3.2 Model structure

The company has developed a de novo cost utility model in Microsoft Excel. It is a cohort-based partitioned survival model comprising three mutually exclusive health states: progression-free, progressed and death. The structure of the company model is shown in Figure 2.

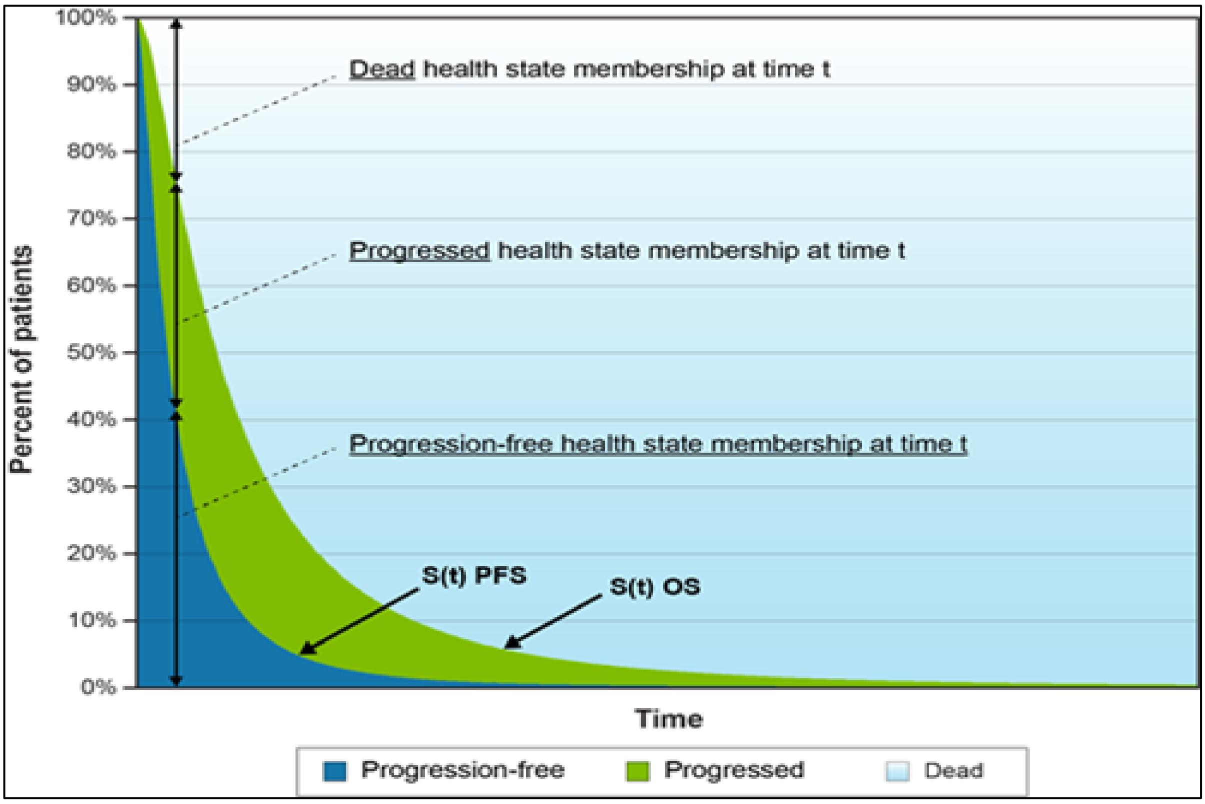


Figure 2 Structure of the company model

PFS=progression-free survival; OS=overall survival; S(t)=survival probability at time t
Source: CS, Figure 32

4.3.3 Population

The modelled population is adults with advanced *RET*+ non-squamous NSCLC who require systemic therapy. This population is in line with the population considered in the LIBRETTO-001 trial, [redacted] and the final scope[28] issued by NICE.

The company has provided results for all patients irrespective of level of tumour PD-L1 expression and for the subgroup of patients with PD-L1 positive NSCLC (i.e., PD-L1 ≥1% subgroup).

The baseline characteristics of the modelled population are shown in Table 24.

Table 24 Modelled baseline patient characteristics

Model parameter	Value	Source
Median age (years)	61.0	LIBRETTO-001 (IAS) (16 December 2019 data cut off)[78]
Percentage female (%)	59.0	
Mean weight (kg)	[redacted]	
Mean body surface area (m^2)	1.81	TA520[23]

IAS=integrated analysis set of the LIBRETTO-001 trial
Source: CS, Table 49

4.3.4 Interventions and comparators

The modelled intervention and comparators are listed in Table 25. This table also includes information about the drug dosages and duration of treatment rules used in the company model.

Table 25 Intervention and comparator dosages in the second-line setting

Drug	Dosage	Duration of treatment
Selpercatinib	160mg twice daily	Until progressive disease or unacceptable toxicity, or other reason for treatment discontinuation
Nintedanib+docetaxel (whole population)	Nintedanib: 200mg twice daily on day 2 to day 21 of every 21-day cycle	Until tumour progression or unacceptable AEs
	Docetaxel: 75mg/m^2 once daily on day 1 of every 21-day cycle	Standard clinical practice is to limit docetaxel to a maximum of 4 cycles per patient in the UK (ERG report, TA347)[25]
Atezolizumab (whole population)	1,200mg once daily on day 1 of every 21-day cycle	Until 2 years or progressive disease or unacceptable toxicity, or other reason for treatment discontinuation
Nivolumab (PD-L1≥1% subgroup)	3mg/kg once daily on day 1 of every 14-day cycle	Until disease progression, up to 2 years
Pembrolizumab (PD-L1≥1% subgroup)	2mg/kg once daily on day 1 of every 21-day cycle	Until disease progression, up to 2 years

Kg=kilogram; mg=milligram; PD-L1=programmed death-ligand 1
Source: CS, Table 47

4.3.5 Perspective, time horizon and discounting

The company states that, in line with the NICE Reference Case,[76] the perspective of the model is the NHS and Personal Social Services (PSS). The cycle length in the company model is 1 week, the time horizon is 25 years, and costs and outcomes are discounted at 3.5% per annum.

4.3.6 Treatment effectiveness and extrapolation

Modelling progression-free and overall survival

The source of selpercatinib data was the phase II component of the single-arm LIBRETTO-001 trial. The company generated pseudo-control (reference arms) using PFS and OS K-M data from the docetaxel+placebo arm of the REVEL trial,[58] adjusted to reflect *RET*+ status using data from the Flatiron database.[75]

As survival data from the LIBRETTO-001 and REVEL[58] trials were not available for the whole model period, the company modelled survival using parametric functions that were fitted to the available trial data and to the pseudo-control (reference) arm OS and PFS data. For the comparators, survival was estimated by applying the HRs generated by the company OS and PFS NMAs to the pseudo-control (reference) arm extrapolations (Table 26). The exception was PFS for patients treated with atezolizumab; as PFS data for patients treated with atezolizumab in the second-line setting were not available, the company assumed that the PFS efficacy of atezolizumab was equivalent to that of pembrolizumab.

Table 26 Hazard ratios used by the company to adjust reference docetaxel+placebo estimates to represent the survival of patients receiving comparator treatments

Treatment	PFS	OS
Nintedanib+docetaxel	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Nivolumab (PD-L1 ≥1% subgroup)	[redacted]	[redacted]
Pembrolizumab (PD-L1 ≥1% subgroup)	[redacted]	[redacted]

OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival
Source: CS, Table 53

Details provided in Table 27 show the different parametric functions that were fitted to the LIBRETTO-001 trial and pseudo-control (reference) arm data. To assess which function had the best fit to trial data, goodness of fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) were generated. In addition, fit was assessed visually, and clinical opinion was sought to assess the long-term plausibility of each function. The company first explored functions to which the PH assumption applied (exponential, Gompertz and Weibull functions). However, for both PFS and OS, it was deemed that separate models fitted to the selpercatinib and reference (and comparator) arms would produce more plausible results.

Table 27 Functions fitted to trial progression-free and overall survival Kaplan-Meier data

	Unstratified*	Stratified	Spline
Selpercatinib arm	Exponential Weibull Gompertz Log-normal Log-logistic Gamma	Weibull Gompertz Log-normal Log-logistic Gamma	One knot, two knots and three knots
Reference arm**	Exponential Weibull Gompertz	Weibull Gompertz	One knot, two knots and three knots

* With treatment as an indicator variable
** Only functions that meet the proportional hazard function were fitted
Source: CS, Table 54 and Table 55

The company reported that, for both PFS and OS, according to AIC/BIC statistics, all survival functions had similar fits to the available selpercatinib and docetaxel+placebo K-M data. For OS, the unstratified exponential function was selected as the most appropriate function to use to model survival for patients receiving selpercatinib and the unstratified Weibull function was selected to model OS for the pseudo-control (reference) arm (and, therefore, comparators). For PFS, a stratified gamma distribution was selected as the most appropriate function to use to model survival for patients receiving selpercatinib and the unstratified Weibull function was selected to model PFS for the pseudo-control (reference) arm (and, therefore, comparators).

Modelling time to treatment discontinuation

The company explored the use of a range of standard parametric distributions to extrapolate LIBRETTO-001 time to treatment discontinuation (TTD) data. However, the company concluded that rather than use a TTD-based extrapolation, it was more plausible to assume that TTD for selpercatinib was the same as PFS. Similarly, TTD data for patients receiving the comparator treatments were modelled to align with PFS. Treatment with docetaxel was capped at four cycles for patients treated with nintedanib+docetaxel, whilst treatment was capped at 2 years for patients receiving atezolizumab, nivolumab (PD-L1 ≥1% subgroup) and pembrolizumab (PD-L1 ≥1% subgroup).

General mortality cap

Age- and gender-specific probabilities of death were taken from published national life tables[1] for England and Wales, using projections for 2018. Life tables were used to ensure that the weekly probability of mortality never fell below that of the general population.

4.3.7 Adverse events

The AE incidence data used in the company model are provided in the CS (Table 57). The AE data for patients receiving selpercatinib, nintedanib+docetaxel, atezolizumab, nivolumab and pembrolizumab and docetaxel were obtained from the LIBRETTO-001 trial, LUME-Lung 1 trial,[70] OAK trial,[62] CheckMate-057 trial,[46] KEYNOTE-010 trial[60] and the REVEL trial,[58] respectively. Grade ≥3 AEs with at least 2% difference in frequency between interventions were included in the model.

4.3.8 Health-related quality of life

Modelling health state utility values in the company model

EORTC QLQ-C30[41] data were collected as part of the LIBRETTO-001 trial. However, the company considered that the baseline utility value (0.9984) obtained from mapping EORTC QLQ-C30 onto EQ-5D-3L,[79] using algorithms published by Khan and colleagues,[80] were too optimistic. The company therefore used the health state utility values that had been used in the NICE Technology Appraisal of nivolumab for previously treated NSCLC (TA484).[26] The utility values in that appraisal were calculated from EQ-5D-3L data collected as part of the CheckMate-057 trial[46] and are shown in Table 28.

Table 28 Base case health state utility values used in the company model

Model health state	Utility value	Source
Progression-free	0.713	NICE TA484[26]
Progressed disease	0.688	

NICE=National Institute for Health and Care Excellence; TA=Technology Appraisal
Source: CS, Table 74

Impact of adverse events on health-related quality of life

The impact of AEs on HRQoL was captured as a one-off QALY loss in the first cycle of the model. The durations and disutilities applied to each AE episode, which were the same for all treatments, were sourced from previous NICE Technology Appraisals[24,26,60,81,82] and are provided in the CS (Table 59).

4.3.9 Resources and costs

The following categories of costs were included in the company model (CS, Section B.3.5):

- intervention and comparator drug acquisition costs
- intervention and comparator drug administration costs
- subsequent drug costs
- health state costs
- AEs costs

- end of life costs.

Costs taken from relevant NICE Technology Appraisals[23,25,26,81,83] were inflated to 2018/2019 prices using the inflation indices provided in the PSSRU Unit Costs of Health and Social Care publication.[84]

Acquisition costs

The drug acquisition costs used in the company model are presented in Table 29. The proposed list price [redacted] currently confidential, so too are the PAS prices for nintedanib, atezolizumab, nivolumab and pembrolizumab.

Table 29 Drug acquisition costs used in the company model

Drug	Form	Strength	Pack size	Cost per pack	Source
Selpercatinib	Capsule	80mg	60	[redacted]	Eli Lilly and Company[85]
Selpercatinib	Capsule	40mg	60	[redacted]	Eli Lilly and Company[85]
Nintedanib+docetaxel					
• Nintedanib	Capsule	100mg	60, 120	£2151.10	BNF (2020)[86]
• Docetaxel	Vial	160mg/ml	8ml	£16.80	eMIT (2019)[87]
Atezolizumab	Vial	60mg/ml	20ml	£3807.69	BNF (2020)[86]
Nivolumab	Vial	10mg/ml	4ml	£439.00	BNF (2020)[86]
Pembrolizumab	Vial	25mg/ml	4ml	£2630.00	BNF (2020)[86]

BNF=British National Formulary; eMIT=electronic market information tool
Source: CS, Table 62

A RDI multiplier was used to reflect dose reductions and any treatment breaks. The RDI for selpercatinib ([redacted]) was taken from the LIBRETTO-001 trial. RDI values were not available for the comparator treatments and hence the company assumed that the RDI for all comparator treatments was the same as the RDI for selpercatinib.

In the base case, the company assumed that wastage occurred for oral drugs (selpercatinib and nintedanib), whereby the cost of 4-week prescriptions were accounted for even if patients discontinued before completing 4 weeks of treatment. In addition, unused content of opened vials of intravenous drugs (docetaxel, atezolizumab, nivolumab and pembrolizumab) were discarded after each treatment. The adjusted cost per dose for each treatment is presented in the CS (Table 64).

Administration costs

The administration costs used in the company model are provided in Table 30.

Table 30 Drug administration costs

Treatment	Mean cost	Source/service code
Selpercatinib	£9.20	NICE TA520;[23] PSSRU (2019) 12 minutes pharmacy time[84]
Nintedanib+docetaxel	£194.20	NICE TA520;[23] PSSRU (2019) 12 minutes pharmacy time);[84] NHS Reference Costs (2018/19) SB12Z[88]
Atezolizumab	£185.00	NICE TA520;[23] NHS Reference Costs (2018/19) SB12Z[88]
Nivolumab	£185.00	
Pembrolizumab	£185.00	

NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSSRU=Personal and Social Services Research Unit; TA=Technology Appraisal
Source: CS, Table 66

Subsequent therapies

In the company base case, the proportion of patients who accrued additional treatment costs due to receiving subsequent lines of treatment when they transitioned into the 'progressed' health state and the duration of these treatment(s) were obtained from previous NICE Technology Appraisals (TA347[25] and TA520[23]). Subsequent treatments were categorised as selpercatinib, immunotherapy or chemotherapy. The subsequent treatments received by patients who had received selpercatinib in the second-line setting were assumed to be the same as the treatments received by patients who had received an immunotherapy in the second-line setting. The cost estimates for the proportions of patients expected to receive each type of subsequent therapy after second-line treatment are presented in Table 31.

Table 31 Subsequent therapy costs

Drug	Mean cost	Proportions of patients treated with each type of subsequent therapy		
		Selpercatinib	Immunotherapy	Chemotherapy
Docetaxel	£765.09	14.9%	14.9%	0.0%
Carboplatin	£1,215.60	8.7%	8.7%	25.0%
Gemcitabine	£2,925.86	7.7%	7.7%	7.7%
Erlotinib	£4,136.30	5.5%	5.5%	5.5%
Pemetrexed	£8,976.06	4.9%	4.9%	0.0%
Vinorelbine	£3,946.53	5.1%	5.1%	5.1%
Radiotherapy	£7,717.50	55.0%	55.0%	56.6%
Subsequent therapy costs		**£5,560.15**	**£5,560.15**	**£5,330.72**

Source: CS, Table 68 and Table 74

Health state costs

The company model was populated with the (inflated) medical resource use costs that were used in the company model that informed NICE TA520.[23] The per cycle cost for the progression-free health state was £141.03, whilst the per cycle costs for progressed health state was £128.59 (see CS, Table 70 for further details).

Adverse event costs

The unit cost associated with each AE and the source of each cost are reported in the CS (Table 71). All but one of the cost estimates were derived using information from previous NICE Technology Appraisals[23,26,83,89] and/or assumptions, along with NHS Reference Costs[88] and costs used in previous NICE Technology Appraisals and/or assumptions.[23,26,83,89]

End of life costs

A one-off end of life cost was applied to each patient who transitioned to the 'Dead' health state. The cost of end of life treatment at a hospital, hospice or at home, and the proportion of patients using each service were taken from the estimates presented in NICE TA520.[23] The one-off end of life treatment cost used in the model was £3,630.88 (see CS, Table 73 for details).

Cost of genetic testing for *RET* fusion status

The company assumed that the cost of genetic testing would be absorbed by the health care system and, therefore, this cost was not included in the company's base case analysis.

5 COST EFFECTIVENESS RESULTS

5.1 *Base case incremental cost effectiveness analysis results*

The company provided an updated version of their model as part of their clarification response. The results presented in this section have been generated using the updated model and, therefore, do not match the results provided in the CS (Section B.3.7).

The company pairwise and fully incremental deterministic base case cost effectiveness analysis results for the population irrespective of tumour PD-L1 level of expression are provided in Table 32 and Table 33 respectively. (Note that nintedanib+docetaxel is only recommended by NICE as an option for the treatment of NSCLC of adenocarcinoma histology).[25] The pairwise cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel and versus atezolizumab are [redacted] and [redacted] per QALY gained respectively.

Table 32 Pairwise deterministic base case results for all-patients (list prices)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	Pairwise versus selpercatinib
Selpercatinib	[redacted]	[redacted]	[redacted]				
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life years gained
Source: Company model version 4

Table 33 Fully incremental deterministic base case results for all-patients (list prices)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	Fully incremental
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]				
Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life years gained
Source: Company model version 4

The company pairwise and fully incremental deterministic base case cost effectiveness analysis results for the PD-L1≥1% subgroup are provided in Table 34 and Table 35. The pairwise results for the comparison of selpercatinib versus nivolumab and versus pembrolizumab are [redacted] and [redacted] per QALY gained respectively.

Table 34 Pairwise deterministic base case results (PD-L1 ≥1% subgroup, list prices)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	Pairwise versus selpercatinib
Selpercatinib	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; PD-L1=programmed death-ligand 1; QALY=quality adjusted life years gained
Source: Company model version 4

Table 35 Fully incremental deterministic base case results (PD-L1 ≥1% subgroup, list prices)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	Fully incremental
Nivolumab	[redacted]	[redacted]	[redacted]				
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; PD-L1=programmed death-ligand 1; QALY=quality adjusted life years gained
Source: Company model version 4

5.2 *Probabilistic sensitivity analysis*

The ERG identified an error in the code used in the company model (original and updated versions) to control the selection of utility values and has, therefore, not re-run the company probabilistic sensitivity analyses (PSA) using the company's updated model.

The company base case probabilistic cost effectiveness results (pairwise and fully incremental) for the comparison of selpercatinib versus relevant comparators for the whole population and for the PD-L1≥1% subgroup are provided in the CS (Table 86 and 87 respectively). The company probabilistic results are similar to the deterministic results. The scatterplots for the comparison of selpercatinib versus relevant comparators for the whole population and the PD-L1 ≥1% subgroup are presented in the CS (Figure 50 and Figure 51 respectively) and the corresponding cost effectiveness acceptability curves are presented in

Figure 3 and

[redacted]

Figure 4 respectively.

The proportions of simulations, for the whole population and the PD-L1 ≥1% subgroup, where selpercatinib was considered cost effective at a threshold of [redacted] per QALY gained were [redacted] and [redacted] respectively.

[redacted]

Figure 3 Cost effectiveness acceptability curves for all-patients (list prices)

Source: CS, Figure 50

[redacted]

Figure 4 Cost effectiveness acceptability curves for the PD-L1 ≥1% subgroup (list prices)

Source: CS, Figure 51

5.3 *Deterministic sensitivity and scenario analyses*

5.3.1 Sensitivity analyses

The ERG has not updated the results of the company deterministic sensitivity analyses as updated results will not lead to conclusions that differ from those that can be made based on results presented in the CS.

For comparisons in the whole population (selpercatinib versus nintedanib+docetaxel and versus atezolizumab) and PD-L1 ≥1% subgroup (selpercatinib versus nivolumab and versus pembrolizumab), parameter uncertainty was tested using univariate sensitivity analysis; all model parameters were systematically and independently varied over plausible ranges determined by either the 95% CIs, or ±10% where no estimates of precision were available. For each comparison, the ICERs per QALY gained were recorded at the upper and lower values to produce a tornado diagram (CS, Figures 55 to 58). For each comparator, in the whole population and in the PD-L1 ≥1% subgroup, the most influential parameters were the utility weights that were applied to the progression-free health state for selpercatinib and the comparators.

5.3.2 Scenario analyses

For all four comparisons (selpercatinib versus nintedanib+docetaxel and versus atezolizumab in the whole population, and versus nivolumab and versus pembrolizumab in the PD-L1 ≥1% subgroup), scenario analyses were also carried out in which key structural assumptions were varied (CS, Table 89). For all comparisons, the selection of different distributions for the

LIBRETTO-001 trial OS extrapolation had the biggest impact on the size of cost effectiveness results. For example, for the comparison of selpercatinib versus nintedanib, varying the distribution used to model OS for patients receiving selpercatinib led to changes to the company base case ICER per QALY gain that ranged between -30.92% and 765.19%.

5.4 *Model validation and face validity*

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC. Clinical advice was sought to inform the choice of distributions used to represent patient survival in the base case. Procedures to verify 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. The clinical outcomes predicted by the model were compared with published outcomes for selpercatinib and comparators.

6 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 *Introduction*

6.1.1 Model validation

The company model uses visual basic for applications (VBA) to generate deterministic and probabilistic cost effectiveness results. There is no reason why VBA cannot be used to run a model if the code is sufficiently annotated; however, the company's VBA code was not annotated and this made checking the algorithms problematic. As a result, the ERG is not able to confirm that there are no algorithmic errors in the company model. Nevertheless, the ERG considers that it is likely that the model is generating deterministic results that are consistent with the results expected from using the parameter values chosen by the company.

6.1.2 Clinical effectiveness evidence base

The company has provided evidence to demonstrate the clinical effectiveness of selpercatinib from the single-arm LIBRETTTO-001 trial. The numbers of events reported in the IAS, the dataset used to populate the model, are small and median follow-up times are short. This means that the there is considerable uncertainty around the effectiveness of selpercatinib. The company economic analyses focus on selpercatinib as a second-line treatment; however, the prior treatments received by nearly all of the LIBRETTO-001 trial population do not reflect the current treatment pathway for patients treated in the NHS (184 patients received chemotherapy (100%); [redacted] patients also received an immunotherapy and [redacted] patients, had received MKIs). Evidence from a published study, has demonstrated that treatment effects in phase II trials may be greater than those in phase III trials.[31]

Evidence to demonstrate the effectiveness of comparator treatments has been generated by the company NMAs. However, the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a confirmed *RET*+ NSCLC population. In addition, the ERG has concerns about the validity of the company's pseudo-control (reference) arms that were generated to connect selpercatinib to the OS and PFS networks. In light of these concerns, the ERG considers that definitive conclusions regarding the direction and magnitude of the relative effectiveness of selpercatinib versus comparators cannot be made.

The NMA OS and PFS networks could only be formed by creating pseudo-control (reference) arms. These arms were created using data from the docetaxel+placebo arm of the REVEL[58] trial, adjusted to reflect *RET*+ status using data from the Flatiron database.[75] The ERG has concerns about the adjustments undertaken by the company (Section 3.6.3). Furthermore, the

REVEL[58] trial population had received PDC in the first-line setting, which is not in line with NHS clinical practice.

The company provided cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel, atezolizumab, nivolumab and pembrolizumab. The ERG considers that nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC are the relevant comparators to selpercatinib in the second-line setting for patients who received an immunotherapy as a first-line treatment. The company did not provide any cost effectiveness evidence for the comparison of selpercatinib versus docetaxel, versus pemetrexed+carboplatin or versus PDC. Based on the available information, the ERG generated alternative cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel and versus docetaxel.

6.2 *Summary of ERG company model critique*

The most important comparative clinical effectiveness outcome from the perspective of generating cost effectiveness results is OS (in the company model base case, for the comparison of selpercatinib versus nintedanib+docetaxel, 80%-90% of the QALY gains for patients treated with selpercatinib are driven by gains in OS). The magnitude of uncertainty around OS means that the impact of other areas of uncertainty on cost effectiveness results cannot be determined accurately, although the likely direction of the uncertainty on the cost effectiveness results can be determined. The other areas of uncertainty identified by the ERG are:

- progressed health state utility value
- use of PFS (rather than TTD) to estimate costs of treatment with selpercatinib
- costs of testing for the RET mutation were omitted from the company analyses
- start time of discounting
- PSA utility value code.

Summary details of the ERG's critique of the company model are provided in Table 36.

Table 36 Summary of ERG company model critique

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Population	• Prior treatments received by patients participating in the LIBRETTO-001 and REVEL[58] trials do not wholly match the experience of patients in NHS clinical practice	6.1
Modelling survival (OS and PFS)	• OS data are so uncertain for selpercatinib (single-arm, phase II study; death observed in [redacted] of patients; median follow-up of [redacted]) that the reliability of any long-term projections of OS are unclear • The company has modelled PFS and OS for comparator treatments using results from the NMAs, which the ERG considers should not be used to inform decision making	6.2 3.3
Utility values	• The utility values used in the company model are those used in the base case analysis presented in NICE TA484;[26] however, the progressed health state utility value is higher than the value that the NICE TA484[26] AC considered was most appropriate	6.4.1
Cost of treatment with selpercatinib	• PFS data were used to model TTD for patients receiving selpercatinib. Available data suggest that this approach underestimates the cost of treatment with selpercatinib	6.4.2
Cost of RET fusion testing	• Costs of testing for *RET* fusion status have not been included in the company model. Whilst the magnitude of the impact on cost effectiveness results of including the cost of testing for *RET* fusion status cannot be determined, the exclusion of testing costs is exerting downward pressure on the ICERs per QALY gained for selpercatinib versus any comparator	6.4.3
Discounting	• Discounting starts from the end of the first cycle rather than at the beginning of the second year, as should be the case. Discounting from the first cycle normally leads to results from pair-wise cost effectiveness analyses that unduly favour the treatment that incurs the higher cost during the first year	6.5
PSA	• The model PSA code allowed utility values in the progression-free health state to be lower than the values used in the progressed health state. The ERG has estimated that the progression-free health state utility is lower than the progressed health state utility in approximately one third of the company PSA iterations. The company PSA results are therefore unreliable	N/A
AEs	• AEs have a minimal impact on cost and QALYs and are not a driver of cost effectiveness; however, the ERG notes that the costs of treating the AEs associated with immunotherapies are very low	N/A

AE=adverse event; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; NMA=network meta-analyses; NICE=National Institute for Health and Care Excellence; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; TTD=time to treatment discontinuation
Source: LR*i*G in-house checklist

6.3 *Modelling OS and PFS*

The ERG has concerns about the methods used by the company to model OS and PFS for patients receiving selpercatinib, for those receiving nintedanib+docetaxel and for those receiving docetaxel.

6.3.1 Modelling survival: selpercatinib

Weaknesses of available selpercatinib data

The currently available clinical effectiveness data on the absolute effectiveness of selpercatinib are generated by the single-arm, phase II LIBRETTO-001 trial.

In the LIBRETTO-001 trial, the number of survival events (OS: [redacted] [[redacted]]; PFS: [redacted] [[redacted]]) and median follow up times (OS: [redacted] months, PFS: [redacted] months) mean that the distributions considered by the company to model OS and PFS all fit the available data reasonably well but produce substantial variation in OS and PFS estimates for the post-trial time horizon (24 years). This variation can be seen in the graphs generated by the company (CS, Figure 43 and Figure 40), which have been reproduced in

[redacted]

Figure 5 and Figure 6.

[redacted]

Figure 5 Selpercatinib OS parametric survival function extrapolations in the second-line setting

OS=overall survival
Source: CS, Figure 43

[redacted]

Figure 6 Selpercatinib PFS parametric survival function extrapolations in the second-line setting

PFS=progression-free survival
Source: CS, Figure 40

6.3.2 Modelling survival: nintedanib+docetaxel and docetaxel

Nintedanib+docetaxel

To generate cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel, the company applied HRs (generated by the company NMAs) to the curve fitted to the pseudo-control (reference) arm data (constructed from REVEL[58] trial docetaxel+placebo arm data adjusted to reflect RET+ status using data from the Flatiron database[75] and other prognostic factors, using the TMLE technique).

The ERG considers that company NMA results should not be used to inform decision making (Section 3.6). Furthermore, the company nintedanib+docetaxel OS and PFS NMA results are counterintuitive. These results, which showed no statistically significant difference between nintedanib+docetaxel and docetaxel+placebo for any outcome, are contrary to LUME-Lung 1 trial[70] results, which show that, compared with docetaxel+placebo, treatment with nintedanib+docetaxel results in statistically significantly improvements in OS and PFS. The company nintedanib+docetaxel NMA results are also contrary to life year (and QALY) estimates generated by the ERG preferred scenario for NICE TA347,[25] which showed that, compared with docetaxel, treatment with nintedanib+docetaxel led to gains in life years and QALYs of 0.224 and 0.140 respectively.

The ERG considers that these NMA results should not be used in the company model and that the most appropriate approach to generating cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel is to use the company pseudo-control (reference) arm data to model nintedanib+docetaxel (by setting the OS and PFS HRs to one) and then adding a 0.140 QALY gain to the incremental QALY result (and 0.224 to the incremental life years result). The ERG highlights concerns about the methods used to generate the pseudo-control (reference) arm (Section 3.6).

Docetaxel

The company model is not designed to produce results for a comparison of selpercatinib versus docetaxel; however, survival data (OS and PFS) for docetaxel+placebo were included in the company model in the form of the pseudo-control (reference) arm data. The ERG has used the reference arm survival data as a proxy for docetaxel survival data. However, the ERG has not been able to confidently model docetaxel treatment and administration costs; therefore, results from this analysis should only be considered exploratory.

6.3.3 Curve selection

The company has used statistical distributions to model OS and PFS for patients receiving the intervention and comparator treatments. The company fitted a range of different distributions to LIBRETTO-001 trial and pseudo-control (reference) arm OS and PFS K-M data and then generated AIC and BIC statistics; AIC and BIC statistics can be used to inform the selection of the most appropriate distributions to use to model OS and PFS. The AIC statistics were calculated jointly for distributions fitted to the LIBRETTO-001 trial data and reference arm K-

M data, as were the BIC statistics. As survival estimates for nintedanib+docetaxel were generated by applying NMA OS and PFS HR results to the distributions fitted to the pseudo-control (reference) arm data, the distributions chosen to model the pseudo-control (reference) arm data have direct impact on the modelling of survival for patients receiving nintedanib+docetaxel.

However, the company has ignored their own AIC and BIC rankings when selecting OS and PFS curves. For example, the unstratified exponential curve was chosen to model OS for selpercatinib (rankings: AIC=[redacted], BIC=[redacted]) and the unstratified Weibull distribution was chosen to model OS for the pseudo-control (reference) arm (rankings: AIC=[redacted], BIC=[redacted]). The company's justification for ignoring the AIC and BIC rankings was that advice from one clinical expert was that the long-term OS and PFS projections generated by all distributions for the pseudo-control (reference) arm were likely to overestimate survival and what was important was maintaining the relative treatment effect difference between selpercatinib and the pseudo-control (reference) arm. The ERG considers that this approach to distribution selection is subjective, arbitrary and open to significant bias. The long-term evidence of the effect of selpercatinib on OS and PFS is unknown; furthermore, survival (OS and PFS) for patients in the pseudo-control (reference) arms is also unknown. Thus, the magnitude of any medium- or long-term relative difference in survival for patients in these two groups is also unknown.

The ERG considers that the least biased approach to distribution selection is to use the AIC and BIC statistics and choose the top-ranking distributions, unless these distributions are clinically implausible or are a poor visual fit to the totality of the available K-M data. It is not clear to the ERG why the company calculated combined AIC and BIC statistics rather than independently calculating and ranking AIC and BIC statistics from the K-M data, especially given that the company chose to use different distributions to model OS and PFS for the selpercatinib and pseudo-control (reference) arms. The ERG considered undertaking AIC and BIC analyses separately for each K-M data set; however, given the uncertainties about the reliability of the selpercatinib and pseudo-control (reference) arm data, the ERG considered that selecting curves using independently calculated AIC and BIC statistics would not generate results that were any more reliable than basing selection on the combined AIC and BIC statistics generated by the company.

Given that the AIC and BIC statistics were calculated for selpercatinib and docetaxel jointly, the distributions chosen should be the same for selpercatinib and docetaxel. Based only on AIC and BIC rankings, the ERG considers that stratified log-normal distributions should be used to generate cost effectiveness results (OS ranking: [redacted], [redacted]; PFS ranking: [redacted], [redacted]). The ERG highlights that the PFS distributions that ranked above the stratified log-normal distribution overestimate PFS for selpercatinib at the end of the period of time that LIBRETTO-001 trial PFS K-M data are available.

Use of the stratified log-normal distribution leads to the OS and PFS HRs for docetaxel falling marginally below those of selpercatinib [redacted]. Whilst it is plausible that OS and PFS hazards will become equal at some point, the ERG took a conservative approach and modelled OS and PFS for patients receiving docetaxel so that the progression and death hazards for these patients (and therefore also for patients receiving nintedanib+docetaxel) were never lower than the progression and death hazards of patients receiving selpercatinib.

The company model does not include an option that allows OS and PFS for patients receiving nintedanib+docetaxel to be modelled using stratified log-normal distributions, although this is an option for docetaxel (the pseudo-control [reference] arm). The ERG, therefore, modelled OS and PFS for patients treated with nintedanib+docetaxel by fitting stratified log-normal distributions to pseudo-control (reference) arm data and then added an extra QALY gain. The ERG approach to modelling survival for patients receiving nintedanib+docetaxel is described in more detail in Section 6.3.2.

The company and ERG choices of distributions to model OS and PFS are shown in Figure 7 and Figure 8 respectively. Compared with company distribution choices, the ERG distribution choices increase OS and PFS for selpercatinib, docetaxel+nintedanib and docetaxel but reduce the relative OS and PFS advantages of treatment with selpercatinib. The ERG highlights that whilst survival for patients receiving nintedanib+docetaxel or docetaxel at 5 years is high ([redacted]) compared to published survival rates for other NSCLC populations (for example, 2 year survival for European patients participating in the LUME-Lung 1 trial[70] was 25.3% for patients with Stage IIIB/IV recurrent NSCLC receiving nintedanib+docetaxel as a second-line treatment), whether it is optimistic or pessimistic for patients with *RET*+ NSCLC treated in the second- or later-line setting after receiving prior immunotherapy is not known.

[redacted]

Figure 7 PFS for selpercatinib, docetaxel+nintedanib and docetaxel (company base case and ERG alternative)

ERG=Evidence Review Group; KM=Kaplan-Meier; PFS=progression-free survival
Source: Company model version 2 and ERG analyses using company model data

[redacted]

Figure 8 OS for selpercatinib, and docetaxel+nintedanib docetaxel (company base case and ERG alternative)

ERG=Evidence Review Group; KM=Kaplan-Meier; OS=overall survival
Source: Company model version 2 and ERG analyses using company model data

6.4 *Other areas of uncertainty*

6.4.1 Utilities

In the absence of utility values based on data collected from patients with advanced, non-squamous *RET*+ NSCLC treated in the second- or later-line settings, the company used base case utility values from NICE TA484;[26] TA484[26] is the NICE appraisal of nivolumab as a treatment option for previously treated non-squamous NSCLC. The NICE TA484[26] base case progression-free and progressed health state utility values are 0.713 and 0.688 respectively. However, the NICE TA484[26] Appraisal Committee (AC) considered that the progressed health state utility value (0.688) was too high and the final AC decision was based on cost effectiveness results generated using the AC preferred value of 0.569. The ERG considers that if utility values from NICE TA484[26] are to be used in the company model for this appraisal, then the chosen values should be those preferred by the NICE TA484[26] AC. Using the NICE TA484[26] AC preferred progressed health state utility value of 0.569 results in an ICER for the comparison of selpercatinib versus nintedanib+docetaxel of [redacted] per QALY gained.

6.4.2 Costing assuming treatment to progression rather than using TTD data

The company has assumed that patients receive treatment with selpercatinib until disease progression (i.e., PFS=TTD). A comparison of PFS and TTD data from the LIBRETTO-001 trial shows that this is not an appropriate assumption; up until 10 months, the TTD data lie below the PFS data but after 10 months the TTD data lie above the PFS data. At 12 months, the LIBRETTO-001 trial data show that [redacted] of patients are progression-free but [redacted] are still on treatment. The ERG is aware that during the first months of a trial some patients will stop treatment with the study drug due to intolerability but patients who tolerate treatment may remain on treatment beyond progression if clinicians believe these patients are still deriving benefit from treatment.

The ERG considers that TTD data, rather than PFS data, should be used to model the length of time that patients receiving selpercatinib spend on treatment; this option is available in the company model. The company has fitted a selection of distributions to LIBRETTO-001 trial TTD data and generated associated AIC and BIC statistics (CS, Appendix J); an exponential distribution ranked first for both AIC and BIC. The ERG has therefore carried out an exploratory analysis using the exponential distribution to model TTD for patients treated with selpercatinib. LIBRETTO-001 trial PFS and TTD K-M data and model PFS and TTD representations (exponential distributions) are displayed in Figure 9.

[redacted]

Figure 9 LIBRETTO-001 trial PFS and TTD Kaplan-Meier data and model PFS and TTD representations (exponential distributions)

KM=Kaplan-Meier; PFS=progression-free survival; OS=overall survival; TTD=time to treatment discontinuation
Source: Company model version 4

The company did not have access to K-M TTD data for patients treated with nintedanib+docetaxel or those treated with docetaxel. The company's approach to modelling TTD data for these treatments was to assume that TTD=PFS. During NICE TA347[25] (nintedanib+docetaxel), the ERG carried out a scenario using TTD data rather than PFS data as the basis of costing treatment with nintedanib+docetaxel and found that this change only slightly reduced the cost of treatment. The ERG therefore considers that using PFS data as a proxy for TTD data is reasonable when estimating the cost of treatment with nintedanib+docetaxel.

Using TTD rather than PFS to model treatment duration for patients receiving selpercatinib, and assuming TTD=PFS for patients receiving nintedanib, results in an ICER for the comparison of selpercatinib versus nintedanib+docetaxel of [redacted] per QALY gained.

6.4.3 Cost of testing for *RET* fusion status

Costs of testing for RET fusion status have not been included in the company model. The ERG considers that testing is a necessary pre-requisite to prescribing selpercatinib and unless costs are covered by the (planned) Genomic Hubs, as suggested by the company, the costs of testing should have been included in the economic model. The ERG could not identify costs of testing for *RET* fusion status but the costs are likely to be significant as the incidence of *RET*+ NSCLC is approximately 1% to 2%[5] of the non-squamous NSCLC population and therefore between 50 and 100 patients would need to be tested to identify one patient eligible for treatment with selpercatinib. Whilst the magnitude of the impact on the ICER per QALY gained of including the cost of testing for *RET* fusion status cannot be determined, the exclusion of testing costs is exerting downward pressure on the ICER per QALY gained for selpercatinib versus any comparator.

6.5 *Impact on the company base case results of ERG model amendments*

At clarification, following the identification of algorithm errors, the company provided a revised version of the company model and, therefore, the company base cost effectiveness results presented in Table 37 and Table 38 do not match those in the CS (but do match the base case results presented in Section 5 of the ERG report which were also generated using the updated model).

The ERG has made the following amendments to the company base case analysis:

- discounted costs and benefits at the start of the second year (B1)
- re-modelled OS and PFS for patients receiving selpercatinib, nintedanib+docetaxel and docetaxel (B2)
- used the NICE TA484[26] AC preferred progressed health state utility value (B3)
- costed treatment with selpercatinib using LIBRETTO-001 trial TTD K-M data (B4).

Given the uncertainty around the OS and PFS projections for selpercatinib, nintedanib+docetaxel and docetaxel, the cost effectiveness results generated by the ERG should not be considered robust; they should only be considered to be more reflective of the available evidence than the results generated by the company. The ERG further cautions that ERG results are optimistic as:

- model PFS and OS estimates for patients receiving selpercatinib are based on data from a phase II, single-arm trial (evidence[31] suggests that phase II trials lead to greater effectiveness benefits than phase III trials) and only a small number of LIBRETTO-001 survival events have occurred
- the costs of testing for *RET* fusion status have not been included in the ERG cost effectiveness analyses.

Details of how the ERG revised the company model are presented in Appendix 9.3 of this ERG report. The cost effectiveness results generated by these amendments are provided in Table 37 (selpercatinib versus nintedanib+docetaxel) and in Table 38 (selpercatinib versus docetaxel). These results have been generated using list prices for all drugs.

Table 37 ERG scenarios for the comparison of selpercatinib versus nintedanib+docetaxel (list prices)

Scenarios	Selpercatinib			Nintedanib+docetaxel			Incremental			*ICER* (£/QALY gained)
	Cost	Life Years	QALYs	Cost	Life Years	QALYs	Cost	Life Years	QALYs	
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1 Discounting starting at start of year two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2 OS and PFS modelled with stratified log-normal distribution, setting nintedanib+docetaxel OS and PFS equal to docetaxel (reference arm) with additional 0.140 QALY gain and 0.224 life year gain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B3 TA484 committee preferred utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B4 Use of TTD to model treatment duration of selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative ERG base case (B1-B4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; PD=progressed disease; TTD=time to treatment discontinuation; QALY=quality adjusted life year

Table 38 ERG scenario for the comparison of selpercatinib versus docetaxel (list prices)

Scenarios	Selpercatinib			Docetaxel			Incremental			*ICER* (£/QALY gained)
	Cost	Life Years	QALYs	Cost	Life Years	QALYs	Cost	Life Years	QALYs	
Alternative ERG base case (B1-B4) but without 0.140 QALY and 0.224 life year gain added for nintedanib+docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; PD=progressed disease; TTD=time to treatment discontinuation; QALY=quality adjusted life year

6.6 *Conclusions of the cost effectiveness section*

The clinical effectiveness evidence presented by the company is not sufficiently robust to address the decision problem. Over and above this major limitation, the company base case cost effectiveness analysis has the following limitations:

- the selection of distributions to model OS and PFS was based on clinical opinion rather than primarily being informed by best statistical fit
- use of PFS rather than TTD data as the basis for costing treatment with selpercatinib
- whilst the progressed health state utility value used in the company model had been used in the base case analysis provided as part of NICE TA484,[26] this value was higher than the NICE TA484[26] AC's preferred value
- testing for *RET* fusion status has not been included in the ERG cost effectiveness analyses.

The amendments made by the ERG to ameliorate the effect of these company modelling choices has, in all three cases, increased the ICERs per QALY gained for the comparison of selpercatinib versus nintedanib+docetaxel and versus docetaxel. However, the ERG considers that the (unreliable) results generated by the ERG are more consistent with the available (unreliable) effectiveness data than those generated by the company base case.

7 NICE END OF LIFE CRITERIA

The company considers that the NICE End of Life criteria[76] apply to the current appraisal of selpercatinib (Table 39). The company's and the ERG's assessments are provided in Table 39. The ERG considers that, based on the evidence presented by the company, selpercatinib does not meet NICE End of Life criteria.

Table 39 Company and ERG assessment of whether NICE End of Life criteria apply to the current appraisal of selpercatinib

Criterion	Company evidence: model base case estimates	ERG comment
The treatment is indicated for patients with a short life expectancy, normally <24 months	Median and mean OS for patients receiving nintedanib+docetaxel are [redacted] respectively	Implementing the ERG preferred OS distribution for patients receiving nintedanib+docetaxel generates a mean OS of [redacted] (median not evaluable).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median and mean OS for patients receiving selpercatinib are [redacted], respectively, resulting in estimated median and mean extensions to life delivered by selpercatinib, when compared with nintedanib+docetaxel, of [redacted] respectively	Whilst results from the company model suggest that the OS gain for patients receiving selpercatinib could exceed 3 months, without more robust comparative OS data this gain is highly uncertain

ERG=Evidence Review Group; OS=overall survival
Source: CS, Table 44

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9 APPENDICES

9.1 Summary of trials included in the NMAs

A summary of the characteristics of the trials included in the NMAs is provided in Table 40 and a summary of the treatments included in the NMAs is provided in Table 41.

Table 40 Summary of characteristics of trials included in NMAs

Trial Reference (Name)	Phase	Blinding	Location	Duration of follow-up	Population included in NMAs
Aerts et al[54] (NVALT-10)	Phase II	Open-label	Netherlands	Median 19 months	Non-squamous subgroup
Ardizzoni et al[55] (GOIRC 02/2006)	Phase II	Open-label	Italy	Median 22.2 months	Non-squamous subgroup (adenocarcinoma+large cell)
Barlesi et al[56] (JAVELIN LUNG 200)	Phase III	Open-label	Multinational	907 days	Non-squamous subgroup
Borghaei et al[46] (CheckMate 057)	Phase III	Open-label	Multinational	Approximately 29 months	Non-squamous population
Dai et al[47]	Not reported	Not reported	China	Not reported	Non-squamous population
Dittrich et al[48] (H3E-MC-S102)	Phase II	Open-label	Multinational	Not reported	Non-squamous population
Fehrenbacher et al[57] (POPLAR)	Phase II	Open-label	Multinational	Up to 28 months	Non-squamous subgroup
Garassino et al [66] (TAILOR)	Phase III	Open-label	Italy	Median 33 months	Adenocarcinoma subgroup
Garon et al[58] (REVEL)	Phase III	Double-blind	Multinational	Up to 29 months	Non-squamous subgroup
Hanna et al[59] (JMEI)	Phase III	Open-label	Multinational	Median 7.5 months	Non-squamous subgroup
Hanna et al[67] (LUME-Lung 2)	Phase III	Double-blind	Multinational	Up to 30 months	Adenocarcinoma subgroup
Herbst et al[60] (KEYNOTE-010)	Phase II/III	Open-label	Multinational	Approximately 23 months	Non-squamous subgroup
Karampeazis et al[61] (CT/06.05)	Phase III	Open-label	Greece	Median 29 months	Non-squamous subgroup
Kim et al[68] (INTEREST)	Phase III	Open-label	Multinational	Median 7.6 months	Adenocarcinoma subgroup
Kim et al[45] (GIRBA-1739)	Phase II	Open-label	Korea	Medan 60.6 months	Non-squamous subgroup
Lee et al[49] (H3E-MC-S103)	Phase II	Open-label	Multinational	Up to 45.5 months	Non-squamous population
Li et al[50]	Phase II	Open-label	USA	Not reported	Non-squamous population
Maruyama et al[69] (V-15-32)	Phase III	Open-label	Japan	Median 21 months	Adenocarcinoma subgroup

Neal et al[51] (ECOG-ACRIN 1512)	Phase II	Open-label	USA	Median 17 months	Non-squamous population
Ramalingam et al[44] (ARCHER)	Phase III	Double-blind	Multinational	Median 7.1 months	Adenocarcinoma subgroup
Reck et al[70] (LUME-Lung 1)	Phase III	Double-blind	Multinational	Median 48 months	Adenocarcinoma subgroup
Rittmeyer et al[62] (OAK)	Phase III	Double-blind	Multinational	Median 28 months	Non-squamous subgroup
Scagliotti et al[63] (SUN1087)	Phase III	Double-blind	Multinational	Median 22 months	Non-squamous subgroup
Sun et al[71] (KCSG-LU08-01)	Phase III	Open-label	Korea	Median 15.9 months	EGFR-subgroup
Takeda et al[52] (AvaALL)	Phase II	Open-label	Japan	Median 11.2 months	Non-squamous population
Urata et al[72] (WJOG 5108L)	Phase III	Open-label	Japan	Median 26.5 months	EGFR-wild type subgroup
Wu et al[64] (Checkmate 078)	Phase III	Open-label	Multinational	Median 10.4 months	Non-squamous subgroup
Yoh et al[65] (I4T-JE-JVCG)	Phase II	Double-blind	Japan	Up to 23 months	Non-squamous subgroup
Zhou et al[53] (CTONG0806)	Phase II	Open-label	China	Median 10.6 months	Non-squamous population
Drilon et al[40] (LIBRETTO-001)	Phase II	Open-label	Multinational	Median [redacted] months	*RET*+ population

EGFR= epidermal growth factor receptor NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; *RET*=rearranged during transfection; *RET*+= *RET* fusion positive
Source: Extracted and adapted from CS; Table 35 (Appendix D), Reference pack: Second Line SLR documents

Table 41 Summary of treatments included in NMAs

Trial Reference (Name)	Treatment arm 1		Treatment arm 2		Treatment arm 3		Total (N)	Outcomes reported		
	Intervention	n[a]	Intervention	n[a]	Intervention	n[a]		OS	PFS	ORR
Aerts et al[54] (NVALT-10)	Erlotinib	73	Erlotinib+ pemetrexed	82	NA	NA	155	Yes	Yes	Yes
Ardizzoni et al[55] (GOIRC 02/2006)	Pemetrexed	93	Pemetrexed+ carboplatin	90	NA	NA	183	Yes	Yes	No
Barlesi et al[56] (JAVELIN LUNG 200)	Avelumab	176	Docetaxel	173	NA	NA	349	Yes	Yes	No
Borghaei et al[46] (CheckMate 057)	Nivolumab	292	Docetaxel	290	NA	NA	582	Yes	Yes	Yes
Dai et al[47]	Pemetrexed	23	Gefitinib	23	NA	NA	46	No	Yes	Yes
Dittrich et al[48] (H3E-MC-S102)	Pemetrexed	83	Erlotinib+ pemetrexed	76	NA	NA	159	Yes	Yes	Yes
Fehrenbacher et al[57] (POPLAR)	Atezolizumab	95	Docetaxel	95	NA	NA	190	Yes	No	No
Garassino et al [66] (TAILOR)	Docetaxel	83	Erlotinib	69	NA	NA	152	Yes	Yes	No
Garon et al[58] (REVEL)	Ramucirumab+ docetaxel	465	Placebo+ docetaxel	447	NA	NA	912	Yes	Yes	Yes
Hanna et al[59] (JMEI)	Pemetrexed	205	Docetaxel	194	NA	NA	399	Yes	Yes	Yes
Hanna et al[67] (LUME-Lung 2)	Nintedanib+ pemetrexed	335	Placebo+ pemetrexed	335	NA	NA	670	Yes	Yes	Yes
Herbst et al[60] (KEYNOTE-010)	Pembrolizumab[b]	684	Docetaxel	240	NA	NA	924	Yes	Yes	No
Karampeazis et al[61] (CT/06.05)	Pemetrexed	130	Erlotinib	127	NA	NA	257	No	Yes	No
Kim et al[68] (INTEREST)	Gefitinib	395	Docetaxel	402	NA	NA	797	Yes	No	No
Kim et al[45] (GIRBA-1739)	Pemetrexed	29	Gefitinib	31	NA	NA	60	Yes[c]	Yes[c]	Yes
Lee et al[49] (H3E-MC-S103)	Erlotinib+ pemetrexed	78	Erlotinib	82	Pemetrexed	80	240	Yes	Yes	Yes
Li et al[50]	Pemetrexed	25	Pemetrexed followed by erlotinib	52	NA	NA	77	No	Yes	Yes
Maruyama et al[69] (V-15-32)	Gefitinib	192	Docetaxel	198	NA	NA	390	Yes	Yes	No
Neal et al[51] (ECOG-ACRIN 1512)	Erlotinib	38	Cabozantinib	38	Erlotinib+ cabozantinib	35	111	Yes	Yes	Yes

Ramalingam et al[44] (ARCHER)	Dacomitinib	304	Erlotinib	299	NA	NA	603	Yes	Yes	No
Reck et al[70] (LUME-Lung 1)	Nintedanib+ docetaxel	322	Placebo+ docetaxel	336	NA	NA	658	Yes	Yes	Yes
Rittmeyer et al[62] (OAK)	Atezolizumab	313	Docetaxel	315	NA	NA	628	Yes	No	No
Scagliotti et al[63] (SUN1087)	Sunitinib+ erlotinib	290	Placebo+ erlotinib	278	NA	NA	568	Yes	Yes	No
Sun et al[71] (KCSG-LU08-01)	Gefitinib	18	Pemetrexed	20	NA	NA	38	No	Yes	No
Takeda et al[52] (AvaALL)	Docetaxel	50	Docetaxel+ bevacizumab	245	NA	NA	295	Yes	Yes	Yes
Urata et al[72] (WJOG 5108L)	Erlotinib	41	Gefitinib	43	NA	NA	84	No	Yes	Yes
Wu et al[64] (Checkmate 078)	Nivolumab	205	Docetaxel	99	NA	NA	304	Yes	Yes	Yes
Yoh et al[65] (I4T-JE-JVCG)	Ramucirumab+ docetaxel	67	Placebo+ docetaxel	72	NA	NA	139	Yes	Yes	Yes
Zhou et al[53] (CTONG0806)	Pemetrexed	76	Gefitinib	81	NA	NA	157	Yes	Yes	Yes
Drilon et al[40] (LIBRETTO-001)	Selpercatinib	185	Placebo+ docetaxel (pseudo-control arm)	451[d]	NA	NA	636	Yes	Yes	Yes
Total number of participants							10,763	10,261	9148	5684
Total number of trials							30	25	27	18

[a] Number of patients from the population included in the NMA (see Table 40)
[b] Only pooled data were available from the pembrolizumab 2mg/kg and 10kg/mg arms in the PD-L1 subgroup, therefore pooled data is included in the NMAs
[c] HRs and 95% CIs estimated from median OS and PFS values according to the methods of Woods et al[90]
[d] Including 447 patients who were randomised to placebo+docetaxel and four patients who crossed over from ramucirumab+docetaxel to placebo+docetaxel in the REVEL trial[58]
CI=confidence interval' HR=hazard ratio; NA=not applicable (two arm study); NMA=network meta-analysis; ORR=overall response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival
Source: Extracted and adapted from CS; Table 35 (Appendix D to the CS), Reference pack: Second Line SLR documents

9.2 ERG summary and critique of statistical approaches used for the NMAs

A summary and an ERG assessment of the company approach to the NMAs is provided in Table 42.

Table 42 ERG summary and critique of statistical approaches used for the NMAs

Item	ERG assessment	Approach	ERG comments
Was the network of comparators appropriate for OS, PFS and ORR?	No	The networks included comparators to selpercatinib which the company considered were relevant to the decision problem for non-squamous NSCLC: • docetaxel+placebo (pseudo-control arm to connect selpercatinib to the networks) • atezolizumab (included in OS network only) • docetaxel+nintedanib and for patients with tumour PD-L1 expression level ≥1%: • nivolumab • pembrolizumab (included in OS and PFS networks) The following 14 treatments were included in at least one of the networks for OS, PFS or ORR; avelumab, cabozantinib, dacomitinib, docetaxel+bevacizumab, erlotinib, erlotinib+cabozantinib, erlotinib+pemetrexed, gefitinib, nintedanib+pemetrexed, pemetrexed, pemetrexed+carboplatin, pemetrexed followed by erlotinib, ramucirumab+docetaxel, sunitinib+erlotinib (CS; Figure 26, Figure 28, Figure 30). The company notes that the numbers of comparators included in the networks are "…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." (CS, Appendix D.1.4).	The inclusion of additional data from comparators that are not relevant to the decision problem introduces uncertainty into the NMA results. Connected networks of the comparators that the company considered relevant to the decision problem could have been constructed via the control arm of docetaxel (or docetaxel+placebo) to inform OS, PFS and ORR NMAs. However, the ERG notes that regardless of the number of comparators included in the networks and their relevance to the decision problem, uncertainty will remain due to the use of an estimated pseudo-control arm to connect selpercatinib to the networks of studies which do not reflect a confirmed *RET*+ NSCLC population.
Were the data sources used for generating the pseudo-control arm for OS and PFS appropriate?	Partly	To connect the selpercatinib arm of the LIBRETTO-001 trial to the networks for OS and PFS, the company generated a pseudo-control arm using data from 451 NSCLC patients with non-squamous histology who received docetaxel+placebo in the REVEL trial.[58] (response to question A5 of the clarification letter). Data from [redacted] patients (*RET*+ [n=[redacted]] and *RET*- [n=[redacted]]) from the Flatiron database[75] who had received first- and second-line treatment were used to adjust the IPD for OS and PFS "…to be reflective of *RET*+ status." (CS, Appendix D, Section D.1.7).	The ERG agrees with the company that using IPD to generate the pseudo-control arm, rather than aggregate or digitised data, was appropriate. The ERG also agrees that it was appropriate to not attempt to generate a pseudo-control arm using the data from the Flatiron database[75] directly, due to small numbers of pre-treated *RET*+ patients.

Item	ERG assessment	Approach	ERG comments
		Missing data for prognostic covariates (race, disease stage, smoking status, histology) were imputed for [redacted] of patients and ECOG score was imputed for [redacted] of patients from the Flatiron database[75] using multiple imputation methods (response to question A7 of the clarification letter). In response to question A4 of the clarification letter, the company explained that these data were selected as the company has access to the IPD of the REVEL trial[58] and did not have access to IPD from any other trials included in the NMAs. The company also explained that it was not possible to generate a pseudo-control arm using data from the Flatiron database[75] directly, as the number of pre-treated *RET*+ patients included within that database (n=[redacted]) was too small.	The amount of missing data for prognostic covariates within the Flatiron database[75] was small, and imputation methods were appropriate. The ERG does not consider that imputation of missing data is likely to have had an important impact on generation of the pseudo-control arm or on the NMA results. Within the Flatiron database, PFS was defined as physician-reported progression, rather than based on RECIST v1.1 which was the definition used in the LIBRETTO-001 trial and in the REVEL trial.[58] This difference in definition of PFS is likely to have introduced uncertainty into the generation of the pseudo-control arm and therefore the NMA results for PFS.
Were the methods for generating the pseudo-control arm for OS and PFS appropriate?	Unclear	The pseudo-control arm was generated separately for OS and PFS using the data from the REVEL trial[58] in two stages. Firstly, a multivariable analysis of the [redacted] patients from the Flatiron database was conducted "…to provide an estimate of a time acceleration factor for *RET*+ status." (CS, Appendix D.1.7). The following covariates were considered: sex, age, race, stage at initial diagnosis, smoking status, ECOG status, histology, EGFR+, PD-1/PD-L1+, *RET*+, other mutations (ALK, ROS1, BRAF, KRAS), targeted therapy for those EGFR+, PD-1/PD-L1+ or *RET*+, time since initial diagnosis to start of second-line treatment. Following exploratory analyses of distributions of covariates and relationships between covariates, an accelerated failure time (AFT) model was used with time-dependent covariates, interactions between covariates and covariates assumed to have a non-linear relationship with the outcome (OS or PFS) modelled using restricted cubic splines. Weibull, log-normal, log-logistic and	The ERG acknowledges the detailed analyses conducted by the company to attempt to adjust the control arm data of the REVEL trial[58] to reflect *RET*+ status. The ERG considers that the model fit of the parametric survival models considered for OS and PFS was similar (CS, Table 32). However, the ERG notes that the model fit statistics provided by the company (R^2) do not inform whether the fit of each model is adequate and whether overfitting could have occurred. Furthermore, the ERG also considers that overfitting of the parametric survival models is likely given that the multivariable analysis conducted is complex and the number of *RET*+ patients was very small (n=[redacted]) compared to the number of *RET*– patients (n=[redacted]). The ERG is unclear about: the rationale for the use of the TMLE model, which prognostic factors were adjusted for using this method, what is meant by counterfactual survival times in this context and why

Item	ERG assessment	Approach	ERG comments
		gamma parametric survival models were considered. Log-logistic models for OS and PFS were chosen based on model fit statistics (CS, Table 32). Estimated time-acceleration factors (CS, Table 33) were then applied to data from the REVEL trial[58] with recensoring, so that adjusted survival times did not exceed follow-up time within the original data. Secondly, a targeted minimum loss-based estimation (TMLE) model[91] was used to adjust for "other prognostic factors." (CS, Appendix D.1.7). The company clarified that the TMLE method used covariate data from the adjusted REVEL trial[58] control arm data and LIBRETTO-001 trial data to adjust survival estimates and produce two "counterfactual survival curves." (CS, Figure 25 and response to question A8 of the clarification letter). The resulting estimated treatment effects (HRs and 95% CIs) for selpercatinib versus docetaxel+placebo (pseudo-control arm) are provided in Table 34 of the CS. The company acknowledges the inherent uncertainty associated with the process of generating a pseudo control arm, and notes that additional adjustment using the TMLE method may have over-estimated the treatment effect for the pseudo-control arms as the relative difference reduced dramatically compared to the same adjusted selpercatinib arms (CS, Section B.2.8.3).	adjustments have also been made to the OS and PFS data from the LIBRETTO-001 trial. Due to uncertainties regarding the complexity and potential overfitting of the multivariable models, and uncertainties regarding adjustments made by TMLE methods which may have resulted in overestimation of treatment effect in the pseudo-control arms, the ERG does not consider that the estimated HRs and 95% CIs for selpercatinib versus the docetaxel+placebo pseudo-control arms used within the OS and PFS NMAs are sufficiently robust for decision making.
Was generation of pseudo-control arm for ORR appropriate?	Partly	The company did not estimate ORR for a pseudo-control arm adjusted for *RET*+ status as ORR data were not recorded within the Flatiron database.[75] Instead, the raw ORR data in the docetaxel+placebo control arm of the REVEL trial[58] were used in an unadjusted comparison with selpercatinib ORR data from the LIBRETTO-001 trial.	The ERG acknowledges that estimation of ORR comparison between selpercatinib and the pseudo-control arm, adjusted for *RET*+ status, was not possible due to lack of ORR data within the Flatiron database.[75] However, the ERG notes the inherent uncertainty of making comparisons between treatment arms of separate trials, and therefore the uncertainty introduced into the ORR NMA due to this naïve comparison.

Item	ERG assessment	Approach	ERG comments
Were NMA methods for OS, PFS and ORR appropriate?	Yes	The NMA methods are described in the CS (Appendix D.4.7). The company used methods in line with NICE DSU TSD 2[92] and TSD 3[93] and followed methods described in a recently conducted network meta-analysis of interventions for second-line NSCLC.[94] The company considered the following study-level covariates in univariate meta-regression: mean age (centred), proportion of patients with ECOG score ≥1, proportion of patients who were male, and proportion of Asian patients. FE and RE hierarchical exchangeable NMA models (i.e., models that allow treatment effects to vary by covariates independently of the other treatments in the network[94,95]) were used to take account of PD-L1 expression level. Best fitting models were selected based on the lowest DIC value (Table 3, response to question A13 of the clarification letter). The company selected a FE hierarchical exchangeable NMA model adjusted for age for OS and PFS, and a FE hierarchical exchangeable NMA model adjusted for the proportion of Asian participants for ORR.	The ERG considers that the NMA methods and approach for selecting the best fitting model was appropriate. The ERG notes that model fit in terms of DIC was similar for all candidate models described (Table 3, response to question A13 of the clarification letter). The ERG also notes that estimates of between-study standard deviation values (sigma) from candidate RE models are relatively low, suggesting that limited statistical heterogeneity is present within the analyses of OS and PFS (CS, Appendix D, Table 38 and Table 39). The ERG emphasises that due to uncertainties associated with the estimation of treatment effects for selpercatinib versus the docetaxel+placebo pseudo-control arm, it is unclear whether NMA results are sufficiently robust for decision making.
Was inconsistency appropriately assessed in the NMAs?	No	As an assessment of inconsistency within the NMAs, the company compared indirect evidence with direct evidence for comparators included within closed loops (response to question A14 of the clarification letter). The company concluded that there was no statistically significant difference between the indirect and direct evidence for most cases. The company also notes that "…information on the comparability of direct and indirect evidence was not available for any comparators relevant to the decision problem in the second-line NMA, as there were no closed loops within the network involving such comparators."	The ERG notes that as well as loop-specific approaches to assessing inconsistency within closed loops of comparators (as used by the company), inconsistency can be assessed within the entire network of evidence using 'global' approaches or tests.[96,97] The company's NMA results show no statistically significant difference between nintedanib+docetaxel and docetaxel+placebo for any outcome. This is inconsistent with direct evidence from the LUME-Lung 1 trial[70] which shows a statistically significant advantage for nintedanib+docetaxel over docetaxel+placebo for both PFS (HR 0.77, 95% CI: 0.62 to 0.96) and OS (HR 0.83, 95% CI: 0.70 to 0.99). Therefore, the ERG concludes that the OS and PFS NMAs do not appear to be robust to inconsistency

Item	ERG assessment	Approach	ERG comments
Was PH assumption appropriately assessed within the NMAs of OS and PFS?	Yes (PFS) No (OS)	Evidence of PH violation was shown for three trials in the PFS NMA [46,51,58] and for two trials in the OS NMA[46,51] (CS, Appendix D, Table 36). In response to question A15 of the clarification letter, the company presented an NMA for PFS using a fractional polynomial approach (first order and second order). The company presented PFS NMA results for best fitting (according to DIC) first-order (p1 = [redacted]) and second-order (p1 = [redacted], p2 = [redacted]) models (Figure 2 and Figure 3, response to question A15 of the clarification letter). Results of fractional polynomial models indicate that selpercatinib is associated with the greatest PFS compared to relevant comparators up to approximately 15 months. The company deemed that such an approach was not appropriate for OS "…due to the immaturity of selpercatinib OS data" from the LIBRETTO-001 trial.	Although the company notes that only one of the trials showing evidence of PH violation included a comparator relevant to the decision problem (nivolumab),[46] the ERG considers that all data included within the networks, including data from irrelevant comparators, influences all NMA results. The ERG acknowledges the additional analyses conducted by the company as an appropriate alternative approach given evidence of PH violation. The ERG also acknowledges the limitations of performing complex fractional polynomial NMAs on immature OS data, but notes that the impact of PH violation on the results of the OS NMA is unknown.

AFT=accelerated failure time; ALK= anaplastic lymphoma kinase; BIRC=blinded independent review committee; BRAF= B-Raf proto-oncogene; CI=confidence interval; DIC=deviance information criterion; DSU=decision support unit; ECOG=Eastern Cooperative Oncology Group; EGFR= epidermal growth factor receptor; FE=fixed effects; HR=hazard ratio; HTA=health technology assessment; IPD=individual patient data; KRAS= kirsten rat sarcoma; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression free survival; PH=proportional hazards; RE=random-effects; *RET*=rearranged during transfection; ROS1=c-ros oncogene 1; TMLE=targeted minimum loss-based estimation; TSD=technical support document
Source: Extracted from the CS; Section 2.8.2 and Section 2.8.3, Appendix D Section D4, the company's response to the clarification letter, and ERG comment

9.3 *Microsoft Excel revisions made by the ERG to the company's model*

ERG revision number and description	Sheet	Cells	Operation
B1 Discounting from start of year two	PSM	AP35:AP86	Set cell values = 1
		AQ35:AQ86	Set cell values=1
		AP87	=1/(1+$F$14)^((C35-1)/52) Copy formula
		AP88:AP1334	Paste formula
		AQ87	=1/(1+$F$15)^((C35-1)/52) Copy formula
		AQ88:AQ1334	Paste formula
B2 OS and PFS modelled with stratified log-normal distribution, setting nintedanib+docetaxel OS and PFS equal to docetaxel with additional 0.140 QALY gain and 0.224 life year gain	2L NSCLC S(t)	R9	=1
		R10	=IF(M10/M9<L10/L9,R9*(M10/M9),R9*(L10/L9)) Copy formula
		R10:R1308	Paste formula
		Z9	=1

ERG revision number and description	Sheet	Cells	Operation
		Z10	=IF(U10/U9<T10/T9,Z9*(U10/U9),Z9*(T10/T9)) Copy formula
		Z11:Z1308	Paste formula
	Survival – 2L NSCLC	Under “Progression Free Survival” dropdown box “Selpercatinib” and “Estimated control arm” Under “Overall survival” dropdown box “Selpercatinib” and “Estimated control arm”	Select “Stratified Log Normal”
	Results	I19	Add 0.140
B3 TA484 committee preferred utility values	Country-Specific Data 2L NSCLC	F795	=0.569
B4 Use of TTD to model treatment duration of with selpercatinib	Survival – 2L NSCLC	Under “Progression Free Survival” dropdown box “Selpercatinib TTD”	Select option “Exponential”
Generating results for docetaxel	Costs – 2L NSCLC	M26	=100%
	Country-Specific Data 2L NSCLC	I555	=0

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 4 January 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 2: Introduction and background

Issue 1 Treatment options after first-line treatment for pre-treated NSCLC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, Table 2: "Nivolumab (CDF only)"	Please amend as follows: "Nivolumab (PD-L1>1% and CDF only)".	Nivolumab was recommended in the CDF for patients with PD-L1>1%.	The ERG report has been updated as suggested.

Issue 2 Number of patients eligible for treatment with selpercatinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 and 27, Section 2.4.3, Table 3: "ERG estimate of the annual number of cases of *RET*+ NSCLC in England"	Please amend as follows: "In Document A of the CS (Table 23), the company has provided an estimate of the number of patients in England with *RET*+ NSCLC and an estimate for the proportion of these that would be eligible for treatment with selpercatinib. The company estimates that there would be 309 patients with *RET*+ NSCLC in Year 1, [redacted] of which would be eligible for treatment with selpercatinib and rising to [redacted] patients eligible for treatment in Year 5. Both estimates include the use of selpercatinib as a first or subsequent line of treatment. The ERG estimates that 263 patients are likely to be diagnosed with advanced *RET*+ NSCLC in England annually (Table 3).	Please include a description of the company's estimates of *RET*+ NSCLC to provide an accurate comparison to the ERGs estimates for patients with *RET*+ NSCLC in England. Comparing to the company's treatment eligible population does not consider share of market research data and assumptions on testing rates.	The ERG report has been updated as suggested.

Issue 3 Source of clinical effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32: "Data from these 200 patients provide evidence relevant to the final scope[28] issued by NICE."	Please amend as follows: "Data from these 200 patients provide evidence relevant to the final scope[28] issued by NICE, but only evidence from 184 patients that received prior platinum chemotherapy were presented in the CS."	There were 200 patients that had pre-treated, advanced *RET*+ NSCLC that received selpercatinib as a second- or later-line treatment (IAS=184 + SAS2=16). However, only data from 184 patients that received prior platinum chemotherapy were presented in the CS.	The ERG report has been updated as suggested.

Issue 4 Source of clinical effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32: "However, median trial OS follow up for these patients is only [redacted] and very few PFS and OS events have occurred."	Please amend as follow: "However, median trial OS follow up for those patients that received prior platinum chemotherapy is only [redacted] and very few PFS and OS events have occurred."	The median trial OS presented in the report relates to the pre-treated IAS population only, not the IAS + SAS2 populations.	The ERG report has been updated as suggested.

Issue 5 Clinical data to support pre-treated patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33: "All patients in the primary analysis set (PrAS) and the IAS had received prior platinum-based chemotherapy and over half of the patients in the	Please amend as follows: "All patients in the primary analysis set (PrAS) and the IAS had received prior platinum-based chemotherapy and over half of the patients in the PrAS and the IAS had also received prior	In the CS, it was specified that clinical evidence for selpercatinib in pre-treated patients came from the IAS population only. The ERG report presents data from the SAS2	The ERG report has been updated as suggested.

PrAS and the IAS had also received prior immunotherapy. Clinical effectiveness evidence to support the treatment of patients with *RET*+ NSCLC in the second-line setting is only available from [redacted] patients ([redacted] patients had only received prior anti-PD-1 treatment and [redacted] patients had only received prior MKIs). The ERG considers that the clinical effectiveness evidence presented in the CS is insufficient to demonstrate the clinical effectiveness of selpercatinib in the second-line setting as a treatment for *RET*+ NSCLC."	immunotherapy. Clinical effectiveness evidence to support the treatment of patients with *RET*+ NSCLC in the second-line setting is available from 184 patients in the IAS ([redacted] patients had received prior anti-PD-1 treatment and [redacted] patients had received prior MKIs). SAS2 (N=16) was not included in the CS as patients had received prior systemic therapy that did not include platinum-based chemotherapy."	population, which is not relevant for the population indicated in the proposed license for selpercatinib.	

Issue 6 Adjustments made to the networks for prognostic factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35: "The ERG considers that the most relevant comparators to selpercatinib are nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC. However, of these, the company has only presented evidence for the comparison of the effectiveness of selpercatinib versus nintedanib+docetaxel, and versus docetaxel from NMAs. The ERG highlights that the trials included in	Please amend as follows: "The ERG considers that the most relevant comparators to selpercatinib are nintedanib+docetaxel, docetaxel, pemetrexed+carboplatin and PDC. However, of these, the company has only presented evidence for the comparison of the effectiveness of selpercatinib versus nintedanib+docetaxel, and versus docetaxel from NMAs. The ERG highlights that the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a	In the CS, it was specified that the second line NMA was run by adjusting for age in the selected base-case. Other prognostic factors (proportion of patients with Asian ethnicity, ECOG performance score, proportion of male patients) were also tested, but the age adjustment best accounted for heterogeneity. Please refer to Appendix D.4.7 of the CS.	The highlighted sentence has been updated to: "nor have the networks been adjusted for the same prognostic factors associated with *RET*+ NSCLC listed in Appendix D.1.7 used to adjust the pseudo-control (reference) arm."

the networks (other than the LIBRETTO-001 trial) do not reflect a confirmed *RET*+ NSCLC population, nor have the networks been adjusted for any prognostic factors associated with *RET*+ NSCLC."	confirmed *RET*+ NSCLC population~~, nor have the networks been adjusted for any prognostic factors associated with *RET*+ NSCLC~~."		

Issue 7 Other considerations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36: "The company considers (CS, Table 44) that, for patients with pre-treated, advanced *RET*+ NSCLC, selpercatinib satisfies NICE End of Life criteria."	Please amend as follows: "The company considers (CS, Table 44) that, for patients with pre-treated, advanced *RET*+ NSCLC, selpercatinib satisfies NICE End of Life criteria versus nintedanib plus docetaxel."	In the CS, it was specified that selpercatinib met NICE End of Life criteria versus nintedanib plus docetaxel.	The ERG report has been updated as suggested.

Section 3: Clinical effectiveness

Issue 1 ERG appraisal of the company's systematic review methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38, Table 6: "Databases were searched from 01 January 2015 to 3rd of September 2019"	Please amend as follows: "Databases were searched from the 01st January 2015 to the 25th of September 2019"	Clinical evidence in second line non-squamous NSCLC was searched for using electronic databases between 01 January 2015 and 25 September 2019.	The ERG report has been updated as suggested.

Issue 2 LIBRETTO-001 trial phase II analysis sets for patients with pre-treated, advanced *RET*+ NSCLC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41, Table 8: "Patients who satisfied the PrAS criteria and enrolled between 18th June 2019 and 16th December 2019."	Please amend as follows: "All *RET*+ patients treated in LIBRETTO-001 by the 16th December 2019 data cut-off date who met the PrAS criteria, including all PrAS patients"	The current statement in the ERG report implies that IAS patients were distinct from the PrAS Analysis Set. The IAS Analysis Set contained all PrAS patients and those patients enrolled between the 18th of June 2019 and the 16th December 2019.	The ERG has added text to clarify that the IAS includes all patients from the PrAS plus patients who enrolled between 18th of June 2019 and the 16th December 2019.

Issue 3 ERG assessment of statistical approaches used in the LIBRETTO-001 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47, Table 12: "Results of these pre-specified subgroup analyses are presented in the CS (Table 25, Table 26, Table 27)."	Please amend as follows: "Results of these pre-specified subgroup analyses are presented in the CS (Table 23, Table 24, Table 25)."	Incorrect table numbers listed in the ERG report.	The ERG report has been updated as suggested.

Issue 4 Overall response rate and duration of response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50: "Subgroup analyses of ORR and DoR in the PrAS by demographic variables (age, sex, race, ECOG PS, metastatic disease, investigator assessed CNS metastases at baseline), type of *RET* fusion partner, type	Please amend as follows: "Subgroup analyses of ORR and DoR in the PrAS by demographic variables (age, sex, race, ECOG PS, metastatic disease, investigator assessed CNS metastases at baseline), type of *RET* fusion partner, type of *RET* molecular assay used, number of previous therapies and	Incorrect table numbers listed in the ERG report.	The ERG report has been updated as suggested.

of *RET* molecular assay used, number of previous therapies and type of previous therapies used are presented in the CS (Table 25, Table 26 and Table 27)."	type of previous therapies used are presented in the CS (Table 23, Table 24 and Table 25)."		

Issue 5 Safety and tolerability results from the LIBRETTO-001 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53: "Over [redacted] of patients in the NSCLC SAS received a starting dose (the anticipated licensed dose) of 160mg selpercatinib BID."	Please amend as follows: "Over [redacted] of patients in the NSCLC SAS received a starting dose (the anticipated licensed dose) of 160mg selpercatinib BID."	The ERG reports that [redacted] of patients in the NSCLC SAS received a starting dose of 160 mg selpercatinib BID. In total, [redacted] ([redacted]) patients received this as a starting dose.	The ERG report has been updated as suggested.

Issue 6 Hypertension as an adverse event of special interest

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55: "The only AEOSI reported by the company that affected patients in the NSCLC SAS was hypertension; this occurred in [redacted] of patients as a Grade 3 event and in [redacted] of patients as a Grade 4 event."	Please amend as follows: "The only AEOSI reported by the company that affected patients in the NSCLC SAS was hypertension; this occurred in [redacted] of patients as an any Grade event and in [redacted] of patients as a Grade 3-4 event."	The proportion of patients that experience hypertension as an "any Grade event" are incorrectly reported in the ERG report. Please see Table 42 in the CS for reference.	The ERG report has been updated as suggested.

Issue 7 Company NMA results for selpercatinib and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59, Table 20 under "Selpercatinib versus comparator/Docetaxel+placebo": "[redacted]"	Please amend as follows: "[redacted]"	ORR NMA results for selpercatinib vs. comparators were adjusted for the proportion of Asian patients. This adjustment was not made for results when the common comparator in the network was used (docetaxel plus placebo). As such, ORR results for selpercatinib vs. docetaxel plus placebo are different to results for docetaxel plus placebo vs. selpercatinib.	The ORR NMA result has been updated in Table 20 of the ERG report as suggested and footnote 'a' of Table 20 has been amended to: "ORR results for selpercatinib versus comparators were estimated from a fixed-effects hierarchical exchangeable NMA model adjusted for the proportion of Asian patients. ORR results for comparators vs docetaxel+placebo were estimated from an unadjusted fixed-effects NMA model."

Section 4: Cost effectiveness evidence

Issue 1 Components of cost-effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62: "The two key components of the economic evidence presented in the CS are (i) a systematic review to identify data to inform economic modelling decisions and (ii) a	Please amend as follows: "The three key components of the economic evidence presented in the CS are (i) a systematic review to identify data to inform economic modelling decisions, (ii) a systematic review to identify utility and cost data, and (iii) a	The company presented two systematic literature reviews in the submission to support the economic analysis: a SLR of prior economic evaluations in NSCLC (Appendix G) and a SLR to identify relevant cost	The ERG report has been updated as suggested.

report of the company's de novo economic evaluation."	report of the company's de novo economic evaluation."	and utility data (Appendix H).	

Issue 2 Modelled population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66: "The modelled population is adults with advanced *RET*+ NSCLC who require systemic therapy."	Please amend as follows: "The modelled population is adults with advanced *RET*+ non-squamous NSCLC who require systemic therapy."	The company believe it is important to specify that a non-squamous population was included in the economic analysis.	The ERG report has been updated as suggested.

Issue 3 Functions fitted to trial progression-free and overall survival Kaplan-Meier data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 27: "* With treatment as an indicator variable"	The addition of an asterisk to the 'unstratified' header row should be added.	An asterisk is currently not present to indicate that treatment was applied as an indicator variable in the unstratified extrapolations.	The ERG report has been updated as suggested.

Issue 4 Modelling progression-free and overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69: "For PFS, a stratified gamma distribution was selected as the most appropriate function to use to model survival for patients receiving selpercatinib and the Weibull function was selected to model PFS for the pseudo-control (reference) arm (and,	Please amend as follows: "For PFS, a stratified gamma distribution was selected as the most appropriate function to use to model survival for patients receiving selpercatinib and the unstratified Weibull function was selected to model PFS for the pseudo-control (reference) arm (and,	The text currently does not specify whether the stratified or unstratified Weibull function was selected to model PFS for the pseudo-control arm.	The ERG report has been updated as suggested.

therefore, comparators).”	therefore, comparators).”		

Issue 5 Life tables year

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69: “Age- and gender-specific probabilities of death were taken from published national life tables[1] for England and Wales, using projections for 2019.”	Please amend as follows: “Age- and gender-specific probabilities of death were taken from published national life tables[1] for England and Wales, using projections for 2018.”	Incorrect year for life tables used in model cited in ERG report.	The ERG report has been updated as suggested.

Issue 6 Inclusion of drug wastage in the model base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71: “The company assumed that no wastage occurred for oral drugs (selpercatinib and nintedanib) whilst unused content of opened vials of intravenous drugs (docetaxel, atezolizumab, nivolumab and pembrolizumab) were discarded after each treatment.”	Please amend as follows: “In the base case, the company assumed that wastage occurred for oral drugs (selpercatinib and nintedanib), whereby the cost of 4-week prescriptions were accounted for even if patients discontinued prior 4 weeks of treatment. In addition, unused content of opened vials of intravenous drugs (docetaxel, atezolizumab, nivolumab and pembrolizumab) were discarded after each treatment.”	It was erroneously reported in the CS that wastage of oral drugs was not included in the base case analysis. The company confirm that wastage of oral (and IV) drugs was included in the model base case and that a scenario analysis (entitled ‘Minimum price per mg’) was run whereby wastage of oral drugs was not included.	The ERG report has been updated as suggested.

Issue 7 Health state costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73: "The per cycle cost for the progression-free health state was £141.03, whilst the per cycle costs for progressed health state was £128.59 (see CS, Table 69 for further details)."	"The per cycle cost for the progression-free health state was £141.03, whilst the per cycle costs for progressed health state was £128.59 (see CS, Table 70 for further details)."	Incorrect table number listed.	The ERG report has been updated as suggested.

Issue 8 Modelling survival: nintedanib+docetaxel and docetaxel

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82: "To generate cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel, the company applied HRs (generated by the company NMAs) to the curve fitted to the pseudo-control (reference) arm data (constructed from REVEL[58] trial docetaxel+placebo arm data adjusted to reflect *RET+* status using data from the Flatiron database[75])."	Please amend as follows: "To generate cost effectiveness results for the comparison of selpercatinib versus nintedanib+docetaxel, the company applied HRs (generated by the company NMAs) to the curve fitted to the pseudo-control (reference) arm data (constructed from REVEL[58] trial docetaxel+placebo arm data adjusted to reflect *RET+* status using data from the Flatiron database[75], and other prognostic factors, using the TMLE technique)."	The text currently does not specify that the pseudo-control arm was also adjusted for other prognostic factors using the TMLE method, in addition to the *RET+* adjustment using the Flatiron database.	The ERG report has been updated as suggested.

Issue 9 ERG summary and critique of statistical approaches used for the NMAs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104, Table 42: "The company notes that the numbers of comparators included in the networks	Please amend as follows: "The company notes that the numbers of	The statement refers the reader to the wrong section of the CS. The quote presented in the ERG	The ERG report has been updated as suggested.

are "…larger than the number of comparators relevant to this decision problem of this submission, due to the requirements for this NMA to support the HTA processes of multiple countries." (CS, Section B.2.6.2)	comparators included in the networks are "…larger than the number of comparators relevant to this decision problem of this submission, due to the requirements for this NMA to support the HTA processes of multiple countries." (CS, Appendix D.1.4)	report is from the CS Appendix, Section D.1.4.	

ACIC and CIC highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 48: "The most common reason for treatment discontinuation was disease progression (CS, Table 12)."	The most common reason for treatment discontinuation has not been marked as academic in confidence.	"The most common reason for treatment discontinuation was [redacted] (CS, Table 12)."	The ERG report has been updated as suggested.
Page 60: "Results from the LIBRETTO-001 trial showed that selpercatinib was well-tolerated; only a small proportion of patients discontinued treatment due to treatment-related (2.4%) or treatment-emergent (6.4%) AEs."	These percentages have not been marked as academic in confidence.	"Results from the LIBRETTO-001 trial showed that selpercatinib was well-tolerated; only a small proportion of patients discontinued treatment due to treatment-related ([redacted]) or treatment-emergent ([redacted]) AEs."	The ERG report has been updated as suggested.
Page 78: "the prior treatments received by nearly all of the LIBRETTO-001 trial population do not reflect the current treatment pathway for patients treated in the NHS (184 patients received chemotherapy (100%); 100/184 patients also received an immunotherapy and 67/184 patients, had received MKIs)."	The number of patients that had received prior treatment has not been marked as academic in confidence.	"the prior treatments received by nearly all of the LIBRETTO-001 trial population do not reflect the current treatment pathway for patients treated in the NHS (184 patients received chemotherapy (100%); [redacted] patients also received an immunotherapy and [redacted], had received MKIs)."	The ERG report has been updated as suggested.

Page 83: "For example, the unstratified exponential curve was chosen to model OS for selpercatinib (rankings: AIC=13/15, BIC=8/15) and the unstratified Weibull distribution was chosen to model OS for the pseudo-control (reference) arm (rankings: AIC=12/15, BIC=12/15)."	The OS rankings have not been marked as academic in confidence.	"For example, the unstratified exponential curve was chosen to model OS for selpercatinib (rankings: AIC=[redacted], BIC=[redacted]) and the unstratified Weibull distribution was chosen to model OS for the pseudo-control (reference) arm (rankings: AIC=[redacted], BIC=[redacted])."	The ERG report has been updated as suggested.
Page 84: "the ERG considers that stratified log-normal distributions should be used to generate cost effectiveness results (OS ranking: AIC=2/15, BIC=1/15; PFS ranking: AIC=3/15, BIC=4/15)."	The OS and PFS rankings have not been marked as academic in confidence.	"the ERG considers that stratified log-normal distributions should be used to generate cost effectiveness results (OS ranking: [redacted]; PFS ranking: [redacted])."	The ERG report has been updated as suggested.
Page 84: "Use of the stratified log-normal distribution leads to the OS and PFS HRs for docetaxel falling marginally below those of selpercatinib at approximately 5 years"	The comparison between OS and PFS in patients treated with docetaxel versus selpercatinib has not been marked as academic in confidence.	"Use of the stratified log-normal distribution leads to the OS and PFS HRs for docetaxel falling marginally below those of selpercatinib [redacted]"	The ERG report has been updated as suggested.
Page 85: "The ERG highlights that whilst survival for patients receiving nintedanib+docetaxel or docetaxel at 5 years is high (30.6%) compared to published survival rates for other NSCLC populations (for example, 2 year survival for European patients participating in the LUME-Lung 1 trial70 was 25.3% for patients with Stage IIIB/IV recurrent NSCLC receiving	This result from Figure 7, which is marked as commercial in confidence, has not been marked as commercial in confidence in the text.	"The ERG highlights that whilst survival for patients receiving nintedanib+docetaxel or docetaxel at 5 years is high ([redacted]) compared to published survival rates for other NSCLC populations (for example, 2 year survival for European patients participating in the LUME-Lung 1 trial70 was 25.3% for patients with Stage IIIB/IV recurrent NSCLC receiving nintedanib+docetaxel as a	The ERG report has been updated as suggested.

nintedanib+docetaxel as a second-line treatment), whether it is optimistic or pessimistic for patients with RET+ NSCLC treated in the second- or later-line setting after receiving prior immunotherapy is not known.”		second-line treatment), whether it is optimistic or pessimistic for patients with RET+ NSCLC treated in the second- or later-line setting after receiving prior immunotherapy is not known.”	
Page 87: “At 12 months, the LIBRETTO-001 trial data show that approximately 65% of patients are progression-free but approximately 74% are still on treatment.”	These percentages have not been marked as academic in confidence.	“At 12 months, the LIBRETTO-001 trial data show that [redacted] of patients are progression-free but [redacted] are still on treatment.”	The ERG report has been updated as suggested.

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Technical engagement response form

Selpercatinib for RET fusion-positive advanced non-small cell lung cancer [ID3743]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **4 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under '[redacted], all information submitted under [redacted], and all information submitted under '[redacted]. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Hamish Lunagaria
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.	Not applicable

Key issues for engagement

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	NO	Eli Lilly and Company acknowledge the concerns of the Evidence Review Group (ERG) regarding the single-arm design of the LIBRETTO-001 trial.[1] However, as noted by the ERG, there is not an ongoing randomised controlled trial comparing selpercatinib with relevant comparators to the National Health Service (NHS) in pre-treated advanced rearranged during transfection (*RET*) fusion-positive patients to resolve this issue. Therefore, further consideration has been given to the network meta-analyses (NMAs) conducted to compare selpercatinib to relevant comparators in light of the ERG's feedback; please see the Company's response to Issues 5 and 6 for further details.
Key issue 2: LIBRETTO-001 trial survival events and length of follow-up	YES	Eli Lilly and Company acknowledge the ERG's concerns that the progression-free survival (PFS) and overall survival (OS) data presented in the Company's submission may be associated with uncertainty due to their immaturity.[1] Accordingly, survival data from the 30th March 2020 data cut of LIBRETTO-001 are presented in Table 1 below, alongside data from the December 2019 data cut (used in the original Company submission) for ease of comparison. The March 2020 data cut provides data over an additional three-month follow-up period for the 184 patients in the non-small cell lung cancer (NSCLC) Integrated Analysis Set (IAS). The 30th March 2020 data cut also provides data from an additional [redacted] eligible efficacy patients (218 eligible efficacy patients in total) with previously treated *RET* fusion-positive NSCLC. Efficacy data for all patients enrolled as of the 30th March 2020 data cut-off are presented in full in Appendix B, including Kaplan-Meier plots for PFS and OS (Figure 5 and Figure 6, respectively). The additional data provided by the 30th March 2020 data cut are consistent with the PFS and OS estimates presented in the original submission (16th December 2019 data cut) for second line patients with *RET* fusion-positive NSCLC receiving selpercatinib. As of the 30th March 2020, in the IAS population

(including all patients enrolled up to 30th March 2020) there had been 74 progression events (PFS: 74/218 [33.9%]) (Figure 5, Appendix B) with a median PFS of 19.29 months (95% CI: 16.5–not estimable [NE]) by Independent Review Committee (IRC) assessment (Table 1). This compares to [redacted] progression events ([redacted] and a median PFS of [redacted] ([redacted]) as of the 16th December 2019 data cut. The durability of PFS with selpercatinib treatment is supported by the finding that [redacted] ([redacted]) of patients in the IAS who were enrolled as of 17th June 2019 (N=184) remain progression-free ≥12 months after treatment initiation, as of the 30th March 2020, compared to [redacted] as of the 16th December 2019.

The median OS remains NE, with [redacted] of patients in the IAS (N=184) alive as of the 30th March 2020 data cut. In the IAS population (including all patients enrolled up to 30th March 2020), 41 (41/218 [18.8%]) deaths had occurred up to the 30th March 2020 data cut (Figure 6, Appendix B), compared with [redacted] ([redacted]]) deaths up to the 16th December 2019 data cut.

The 30th March 2020 data cut also provides additional data on the objective response rate (ORR) to selpercatinib treatment and the duration of the response (DOR). The ORR as of the 30th March 2020 was [redacted] in the IAS population, which is consistent with the ORR from the 16th December 2019 data cut of [redacted] (Table 1). In NSCLC, there is evidence that improvements in ORR appear to correlate with improvements in OS and PFS.[2, 3] Furthermore, the median DOR in the IAS also remained consistent at 17.5 months (95% CI: 12.1–NE) for all patients enrolled as of the 30th March 2020 data cut, supporting the assertion that treatment with selpercatinib produces a high and durable tumour response that is expected to provide prolonged physical and psychological benefit to patients.

The results presented here from the 30th March 2020 data cut provide further evidence to support the high and durable response rate with selpercatinib, as well as the potential survival benefits of selpercatinib treatment in patients with advanced *RET* fusion-positive NSCLC. The updated results for OS continue to suggest that selpercatinib treatment may confer a survival benefit to this patient group. Data collection from LIBRETTO-001 remains ongoing and subsequent data cuts will become available in due course.

		Table 1. PFS and OS for second line *RET* fusion-positive NSCLC patients (IAS) based on IRC assessment

	All patients enrolled as of 17th June 2019		**All eligible efficacy patients enrolled as of 30th March 2020**
Data cut	**16th December 2019 N=184**	**30th March 2020 N=184**	**30th March 2020 N=218**
PFS			
Status n (%)			
Event	[redacted]	[redacted]	74 (33.9)
Censored	[redacted]	[redacted]	144 (66.1)
Duration of PFS (months)			
Median	19.32	[redacted]	19.29
95% CI	[redacted]	[redacted]	16.5–NE
Minimum, maximum	[redacted]	[redacted]	0.0+, 30.6+
Rate of PFS (%)			
12 months or more	[redacted]	[redacted]	69.7
95% CI	[redacted]	[redacted]	62.2–75.9
OS			
Status n (%)			
Event	[redacted]	[redacted]	41 (18.8)
Censored	[redacted]	[redacted]	177 (81.2)
Duration of OS (months)			
Median	[redacted]	[redacted]	NE
95% CI	[redacted]	[redacted]	25.7–NE
Minimum, maximum	[redacted]	[redacted]	0.3, 34.5+

Rate of OS (%)			
12 months or more	[redacted]	[redacted]	88.1
95% CI	[redacted]	[redacted]	82.5–91.9
ORR (CR + PR)			
N (%)	[redacted]	[redacted]	124 (56.9)
95% CI	[redacted]	[redacted]	50.0–63.6
Duration of response (months)			
Median	[redacted]	[redacted]	17.51
95% CI	[redacted]	[redacted]	12.1–NE
Minimum, maximum	[redacted]	[redacted]	1.8+, 29.8+
Duration of response follow-up (months)			
Median	[redacted]	[redacted]	11.99
25th, 75th Percentiles	[redacted]	[redacted]	7.4, 15.9

Footnotes: Eligible efficacy 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. Censored observations are denoted by '+'.
Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; NE: not estimable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut);[4] : Eli Lilly and Company Ltd. Data on File (30th March 2020 cut).[5]

Key issue 3: Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice **Question for clinical experts:** Do you agree	YES	Eli Lilly and Company acknowledge the issue raised by the ERG regarding the prior treatments received by the LIBRETTO-001 trial population.[1] In accordance with the eligibility criteria for LIBRETTO-001, and as noted by the ERG,[1] [redacted] patients in the IAS population had received at least one prior line of platinum-based chemotherapy and [redacted] had received prior immunotherapy. A smaller proportion of patients in the IAS had also received prior multi-kinase inhibitor (MKI) therapy ([redacted]). Excluding MKI therapy, which Eli Lilly and Company acknowledge is not currently approved for use by the NHS,[6, 7] the prior treatments

that prior treatments received in LIBRETTO-001 trial population do not reflect NHS clinical practice? Please explain.		received by patients in LIBRETTO-001 mirror the therapy regimens currently recommended by NICE in the first line setting in the United Kingdom (UK).[8-11] To address the ERG's concern around prior use of MKIs in the IAS analysis set, Eli Lilly and Company provide survival data for a subgroup of the IAS population, which excludes patients who received prior MKI treatment (N=[redacted]). The patients in this subgroup therefore align more closely with *RET* fusion-positive NSCLC patients in the UK. Data for this subgroup are presented in Table 2 below, with Kaplan-Meier plots for PFS and OS also provided in Figure 7 and Figure 8, respectively, in Appendix C. As of the 30th March 2020 (including patients enrolled up to 30th March 2020), there had been [redacted] progression events in the IAS MKI-naïve subgroup ([redacted]% of patients), with a median PFS of [redacted] months (Figure 7, Appendix C). These results compare to [redacted] progression events in the IAS analysis set overall (N=218) ([redacted]% of patients), with a median PFS of [redacted] months as of March 2020. In addition, there were [redacted] deaths in the MKI-naïve subgroup ([redacted]% of patients) as of 30th March 2020, with a median OS of [redacted] (Figure 8, Appendix C). The estimated median OS in the MKI-naïve subgroup is currently unstable due to the low number of deaths that had occurred as of the 30th March 2020. In the IAS analysis set overall, there were [redacted] deaths ([redacted]% of patients) as of 30th March 2020, whilst the median OS was [redacted]. The PFS and OS results for the IAS MKI-naïve subgroup are consistent with the results for the IAS analysis set overall. As the prior therapies received by this subgroup align with the prior therapies that *RET* fusion-positive NSCLC patients in the UK would typically receive, Eli Lilly and Company consider the results from LIBRETTO-001 to be generalisable to the target patient population in the NHS. Despite the use of MKI treatment in the IAS analysis set, UK clinical experts have also affirmed that the patient population in the LIBRETTO-001 trial is otherwise generalisable to clinical practice in the UK overall.[12]

Table 2. PFS and OS for second line *RET* fusion-positive NSCLC patients (IAS and IAS MKI-naïve subgroup) based on IRC assessment

Characteristic	IAS N=218	IAS MKI-naïve subgroup [redacted]
PFS		
Status n (%)		
Event	74 (33.9)	[redacted]
Censored	144 (66.1)	-
Duration of PFS (months)		
Median	19.29	[redacted]
95% CI	16.5–NE	-
Minimum, maximum	0.0+, 30.6+	-
OS		
Status n (%)		
Event	41 (18.8)	[redacted]
Censored	177 (81.2)	-
Duration of OS (months)		
Median	NE	[redacted]
95% CI	25.7–NE	-
Minimum, maximum	0.3, 34.5+	-

Footnotes: Eligible efficacy 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. Censored observations are denoted by '+'.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MKI: multi-kinase inhibitor; NE: not estimable; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File (30th March 2020 cut).[5]

Eli Lilly and Company also acknowledge the ERG's request for data to show whether patients who received platinum-based chemotherapy and immunotherapy received these treatments consecutively or simultaneously.[1] The IAS analysis set of LIBRETTO-001 is comprised of pre-treated patients of mixed

		treatment lines, including patients at second line, third line and later lines of treatment. For this reason, it is not possible for Eli Lilly and Company to provide data showing whether patients received platinum-based chemotherapy and immunotherapy consecutively or sequentially. However, the Company has provided a more detailed breakdown of the types of prior treatments received by patients in the IAS analysis set in Table 20, Appendix C.
Key issue 4: Relevant comparator treatments **Question for clinical experts:** Considering current standard care, do you agree with the ERG that docetaxel (with or without nintedanib) are the most relevant comparators for selpercatinib in the second-line setting? Please explain.	NO	Eli Lilly and Company have considered the ERG's rationale relating to the relevant comparators for selpercatinib in the second line setting in the NHS.[1] As the ERG highlighted, clinical advice to Eli Lilly and Company indicates that in clinical practice, patients with *RET* fusion-positive NSCLC who receive an immunotherapy at first line would not typically be treated with another immunotherapy in the second line setting. Market research conducted by Eli Lilly and Company indicates that there is a high usage of immunotherapies in the first line setting in the UK (please see Document B, Section B.1.3.2), meaning only a small proportion of *RET* fusion-positive NSCLC patients would be likely to receive immunotherapies such as atezolizumab, nivolumab and pembrolizumab at second line. Eli Lilly and Company therefore agree with the ERG that immunotherapies should not be considered as relevant comparators to selpercatinib in the second line setting. The ERG have noted that pemetrexed plus carboplatin and platinum doublet chemotherapy may also be considered relevant comparators to selpercatinib in the second line setting.[1] However, market share data provided by Eli Lilly and Company in the original submission (Document B; Section B.1.3.2) highlighted a declining use of platinum doublet chemotherapy ([redacted]) and pemetrexed plus carboplatin ([redacted]) as second line therapies for advanced pre-treated non-squamous NSCLC patients in the UK. Two expert clinicians consulted by Eli Lilly and Company also advised that pemetrexed and older chemotherapy regimens are now rarely used in clinical practice. In addition, pemetrexed and platinum-based chemotherapy regimens are frequently used with immunotherapies in the first line setting, which further reduces the likelihood that these therapies will be used at second line.[9, 13] Second line market share data obtained by Eli Lilly and Company indicates that docetaxel monotherapy and nintedanib plus docetaxel both have a moderate share of the market, at [redacted] and [redacted], respectively. Information provided by clinical experts who were consulted during the revisions to the Company's original submission also supports consideration of nintedanib plus docetaxel and docetaxel monotherapy as relevant comparators to selpercatinib in the second line setting. Consequently, Eli Lilly and Company

		agree that the following treatments are relevant comparators to selpercatinib in second line advanced non-squamous and *RET* fusion-positive UK NSCLC patients: • Docetaxel monotherapy • Nintedanib plus docetaxel The NMA and cost-effectiveness results have been updated for selpercatinib versus these two comparators. Updated cost effectiveness results are summarised in Appendix A and the updated results for the NMA are presented in Appendix F.
Key issue 5: The relevance of population participating in the trials that provided comparator evidence for the company NMAs **Question for clinical experts:** Do you consider the result of the indirect comparison of selpercatinib with docetaxel and docetaxel plus nintadenib to be clinically plausible (see table 20 in the ERG report)?	NO	Eli Lilly and Company acknowledge that the trial populations included in the NMA network were likely to have had a low incidence of *RET* fusion-positive patients, given the frequency of *RET* fusions (~1–2%) across all NSCLC cases, which is a limitation of the analysis.[14] However, Eli Lilly and Company were able to adjust the docetaxel plus placebo arm (or pseudo-control arm), for the effect of *RET* on patient survival, using real world evidence data from *RET* fusion-positive and negative patients in the Flatiron CGDB database (please see Section D.1.7 in the Appendices of the Company's original submission for further details). As part of the Company's revised indirect treatment comparison (ITC) approach, described in detail in response to Issue 6, further differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the pseudo-control arm were adjusted for using propensity score matching. It was not possible to control for *RET* in the rest of the network, as the *RET* status of patients in the other studies included in the network was not reported. Nevertheless, as part of the revised ITC Eli Lilly and Company used meta-regression on the network, to relate the size of treatment effects obtained from the meta-analysis to numerical characteristics of the included trials, with the aim of explaining as much of the observed between-trial heterogeneity and mitigating this uncertainty as much as possible. As detailed in Table 21, Appendix D the difference in deviance information criterion (DIC) values between key covariates was <4 in most cases, indicating minimal heterogeneity in the network. This suggested that numerical differences in characteristics between trial populations included the network were unlikely to be having a significant impact on survival outcomes.

		The difference in DIC between the fixed effects (FE) model with no covariates ([redacted]) and the FE model adjusted for age ([redacted]) was >4. However, inclusion of an age adjustment, which was used in the original Company submission, resulted in model overfitting for nintedanib plus docetaxel, which produced unrealistic estimates of OS. Further details can be found under the 'NMA meta-regression and model selection' section, in response to Issue 6. Exclusion of age from the NMA resulted in more clinically plausible OS estimates for nintedanib plus docetaxel versus docetaxel (please see revised NMA results presented in Table 26, Appendix F. While Eli Lilly and Company therefore acknowledge that it was not possible to mitigate all uncertainty related to the low incidence of *RET* in the trial populations included in the network, the Company adopted an approach that endeavored to simulate a clinically relevant population and plausible comparative survival estimates for relevant comparators to selpercatinib, within the confines of the limited data available.
Key issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	YES	Eli Lilly and Company acknowledge the concerns raised by the ERG surrounding the targeted minimum loss-based estimation (TMLE) method.[1] To improve the robustness of the ITC, the methodology has been updated using propensity score matching to estimate treatment effects between selpercatinib and relevant comparators. This approach provided a more clinically plausible PFS estimate for the pseudo-control arm, whilst sample size was not significantly decreased after the matching process. A description of the updated method using propensity score matching is provided below. Relevant code for propensity score matching and the NMA are available in Appendix E. **Propensity score matching approach** As described in the original Company submission (Document B, Section B.2.8), the first step in the generation of the pseudo-control arm was the adjustment for *RET* fusion status using data from the Flatiron Clinico-Genomic database (CGDB). This step remained the same for the revised ITC approach. Full details of the methods used in the analysis of the Flatiron CGDB were presented in the Company's original submission (Appendices, Section D.1.7). Following adjustment of the pseudo-control arm for *RET* fusion status, further differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the docetaxel plus placebo arm from REVEL were adjusted for using propensity score matching with a multivariable regression approach.[15]

		The covariates that were used as adjustment factors during propensity score matching are summarised in Table 3. Adjustment for further prognostic factors beyond *RET* status between the selpercatinib and docetaxel plus placebo arms was necessary to account for any further differences between trial populations, and to generate a reliable treatment effect estimate between the two treatments, such that selpercatinib could be joined to the full network.

A summary of the baseline patient characteristics of the LIBRETTO-001 and REVEL trial populations, alongside data showing the impact of adjustment for *RET* and other prognostic factors is provided in Table 23. Summary of patient characteristics of the REVEL and LIBRETTO pre-treated NSCLC trial populations, before and after adjustment for *RET* fusion status and the propensity score matching process

Characteristic	Baseline characteristics		After *RET* adjustment Before propensity score matching		After propensity score matching[a]
	LIBRETTO-001, IAS (selpercatinib) (N=184)	REVEL (docetaxel + placebo) (N=447)[b]	Selpercatinib arm (N=174)	Docetaxel + placebo arm (N=447)	Docetaxel + placebo arms (N=174)
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology: Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≥ 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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		Time since diagnosis to start of trial (median months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] The analysis followed greedy match as the matching algorithm. [b] A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to generate the pseudo-control arm. [c] The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the need to exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on covariates required for the matching process.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS, Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File.(7)

, Appendix F.

Table 3. Summary of patient characteristics of the REVEL and LIBRETTO trial populations for second-line NSCLC

Characteristic	REVEL (docetaxel + placebo) (N=625)	LIBRETTO PAS (N=105)	LIBRETTO IAS (N=184)
Age (years)			
Median	[redacted]	61	62
Gender (%)			
Female	[redacted]	59.0	57.1
Race (%)			
White	[redacted]	52.4	46.7
Asian	[redacted]	38.1	44.6
Other	[redacted]	[redacted]	[redacted]
Smoking history (%)			
Never smoked	[redacted]	71.4	67.9
Histology (%)			
Non-squamous	[redacted]	[redacted]	[redacted]

ECOG performance score (%)			
ECOG ≥ 1	[redacted]	70.5	64.2
History of prior surgery (%)			
Prior surgery	[redacted]	[redacted]	45.7
Stage at diagnosis (%)			
Stage IV	[redacted]	96.2	92.5
Time since diagnosis to start of trial (months)			
Median	[redacted]	30.1	24.2
Sum of longest diameters of tumors (mm)			
Median	[redacted]	60.0	54.7
Metastatic sites (%)			
≥ 2 metastatic sites	[redacted]	[redacted]	[redacted]
CNS metastases at baseline	[redacted]	35.2	32.6

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group, IAS, integrated analysis set (all patients treated with platinum-based chemotherapy); NR, not reported; NSCLC: non-small cell lung cancer; PAS, Primary Analysis Set.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Propensity score matching uses individual patient data (IPD) from one data set to produce weights 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.[15] Specifically, matching aims to replicate randomisation by identifying control individuals who are similar to the treated individuals in one or more characteristics.[16] By matching the outcomes of individuals who differ in the treatment variable, but are otherwise observationally similar, this approach enables estimation of the treatment effect.[16]

A multivariable regression model was used to estimate propensity scores and match data from the docetaxel plus placebo and selpercatinib arms.[15] Guidance provided in NICE TSD17 informed the propensity score matching process.[16]

		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 treatment effect and estimate log (hazard ratios) and standard errors for selpercatinib versus the pseudo-control arm (Table 4). The hazard ratio was then introduced into the NMA of second line treatments described previously in the Company submission.

Table 4. Estimated treatment effects for selpercatinib versus docetaxel (pseudo-control arm) in second line patients

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

Abbreviations: CrI: credible interval; OS: overall survival; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

The Kaplan-Meier outputs for PFS and OS, from the time acceleration adjustment for *RET* and the adjustment for further prognostic factors through matching using propensity scores, are presented below in Figure 1a and b.

Figure 1. Kaplan-Meier charts for selpercatinib and docetaxel pseudo-control arm in second line advanced NSCLC patients following the time acceleration adjustment for *RET* and propensity score matching

(A) PFS[a]

		[redacted]

(B) OS[a]

[redacted]

Footnotes: [a] The selpercatinib arm was not adjusted for *RET*, as all patients in LIBRETTO-001 were *RET* fusion-positive. In the selpercatinib arm, propensity score matching had little effect on survival outcomes and consequently the ‘original and *RET*-adjusted’ and ‘PSM-adjusted’ selpercatinib curves are superimposed for both PFS and OS.
Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; PSM: propensity score matching; *RET:* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File.[5]

The impact of the adjustment for *RET* fusion and other prognostic factors can be seen to have made the OS estimate for docetaxel more optimistic,[17] whilst the adjustment had little effect on OS in the selpercatinib arm. Clinical opinion suggested that following the revised adjustment process, an artificial

		overestimation of OS remained in the pseudo-control arm ([redacted]). This is supported by a recent observational study that utilised Flatiron CGDB data to compare OS based on *RET* status, before and after adjustment for covariates, which found that despite *RET* fusion-positive patients having favourable OS compared with patients without a *RET* fusion, there were no significant differences in OS based on *RET* status after adjustment for baseline covariates.[18] In addition, median OS for advanced NSCLC patients, without a *RET* fusion, receiving docetaxel has been reported at 9.1 months.[17] Further published data supporting limited survival for non-targeted treatments in pre-treated *RET* fusion-positive NSCLC are presented in response to Issue 12. Altogether, these data support our assertion that OS was overestimated in the pseudo-control arm as a result of the Flatiron *RET* adjustment and propensity score matching (Figure 1). However, the adjustment process had a smaller impact on the PFS estimate for the docetaxel arm, which was considered by clinical experts to be a clinically plausible PFS estimate for the pre-treated advanced non-squamous *RET* fusion-positive NSCLC population. As such, Eli Lilly and Company believe that the updated NMA method, using propensity score matching, provides more robust PFS survival estimates for selpercatinib versus the pseudo-control (reference) arm. Although OS estimates for the docetaxel plus placebo pseudo-control arm remain an overestimation, the impact of this on subsequent cost-effectiveness analyses is that the cost-effectiveness results for selpercatinib are likely to be conservative, as the true difference in treatment effect on OS between selpercatinib and comparators has not been fully realised. **NMA meta-regression and model selection** A meta-regression was explored to relate the size of the treatment effects obtained from the meta-analysis to certain numerical characteristics of the included trials, with the aim of explaining as much of the observed between-trial heterogeneity as possible. In line with the approach taken in the Vickers et al. study,[19] meta-regression was used to explore the following study level covariates: median age, ECOG status ≤1, proportion male, proportion programmed death ligand-1 (PD-L1) positive and proportion Asian. Covariates were included one at a time to see if they improved model fit. Both random effects (RE) and fixed effects (FE) hierarchical exchangeable models were explored for all outcomes. The models, with or without the inclusion of covariates, were assessed for model fit for OS, PFS and ORR, using DIC. Model

		fit statistics for the models explored are included in Table 21, Appendix D. Lower DIC values represent better model fit. The feasibility of conducting a hierarchical exchangeable model, to account for PD-L1 status, was also explored, given the global nature of the NMA and the inclusion of treatments dependent on a patient's PD-L1 status. However, it was not possible to include REs for the hierarchical exchangeable model because of a limited number of parameters; therefore, an FE approach was selected. For OS and PFS, the FE hierarchical exchangeable model that was adjusted for age corresponded to the lowest DIC value, suggesting it had a better fit (see Appendix D, Table 21). This model was used in the original NICE submission. However, visual assessment of the relationship between OS versus age for nintedanib plus docetaxel suggested that there was evidence of overfitting, with increasing age predicting unrealistic estimates of OS. It is difficult for an NMA to accurately predict the effect of a covariate when restricted to summary level data, and therefore the effect of age may have been overestimated by the meta-regression. As such, a cautious approach was taken whereby a FE hierarchical exchangeable model, without age adjustment, was selected for OS and PFS in the revised NMA. For ORR, an FE hierarchical exchangeable model was selected, adjusted for the proportion of Asian patients. **NMA results** Updated results from the NMA, generated using the adjustment for *RET* positive status, the propensity score matching approach described above, a FE hierarchical exchangeable model for OS and PFS, and a FE hierarchical exchangeable model adjusted for the proportion of Asian patients for ORR, are available in Appendix F. The results of the revised NMA have also been incorporated into the cost-effectiveness results presented at Technical Engagement.
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Question for clinical experts:** What	YES	Please see the response to Issue 8 below for additional evidence on the revised survival curves for selpercatinib, docetaxel, and nintedanib plus docetaxel.

proportion of patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with selpercatinib as a second-line treatment? • If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from advanced NSCLC with other molecular drivers?		
Key issue 8: The company modelling of survival for patients	YES	Eli Lilly and Company acknowledge that the ERG's preferred survival function for the docetaxel plus placebo pseudo-control (or reference) arm, based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) rankings, was the stratified lognormal function.[1]

receiving nintedanib+docetaxel **Question for clinical experts**: What proportion of patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with nintedanib+docetaxel or docetaxel as second-line treatments? • If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from		Implementing the ERG's preferred modelling of OS in the Company's original model for patients receiving docetaxel, and subsequently adding a quality-adjusted life year (QALY) gain to represent additional health-related quality of life (HRQoL) and survival benefits associated with nintedanib plus docetaxel, generated a mean OS of [redacted] months for nintedanib plus docetaxel. The 5-year survival for patients receiving nintedanib plus docetaxel or docetaxel monotherapy using the original Company methodology ([redacted]; see Figure 2) is high compared to published survival rates for other NSCLC populations, which the ERG acknowledges. Implementing the ERG's preferred modelling of OS in the Company's revised model for patients receiving docetaxel generates similarly consistently high predicted survival rates for docetaxel ([redacted] at 5 years; see Table 5). The ERG supports their approach by noting that whether the 5-year survival is optimistic or pessimistic for patients with *RET* fusion-positive NSCLC, treated in the second- or later-line setting after receiving prior immunotherapy, is unknown.[1]

advanced NSCLC with other molecular drivers?		**Figure 2. OS for selpercatinib, docetaxel monotherapy and nintedanib plus docetaxel (Company base case and ERG alternative)** [redacted] **Footnotes:** OS extrapolation obtained from the ERG report for selpercatinib in NSCLC, page 86. **Abbreviations:** ERG: Evidence Review Group; KM: Kaplan-Meier; OS: overall survival. Following recommendations from the ERG,[1] Eli Lilly and Company sought further clinical expert opinion regarding survival estimates for pre-treated advanced *RET* fusion-positive NSCLC patients. Two expert clinicians practising in the UK were asked to provide survival estimates for patients receiving selpercatinib or docetaxel monotherapy, who had been previously treated with an immunotherapy. The survival estimates are provided in Table 5 alongside the projections for docetaxel monotherapy using the

		Company's original and revised model, which were generated using the stratified lognormal function, as preferred by the ERG. Clinical expert opinion does not support the ERG survival projections using the stratified lognormal curve for docetaxel. The experts consulted indicated that patients receiving docetaxel monotherapy as second line treatment would be unlikely to survive for more than 24 months on average, and that the NICE End of Life Criterion (for short life expectancy) was expected to be met for this patient population. This is reflected in the survival estimates provided by the two clinicians in Table 5, where [redacted] of *RET* fusion-positive patients receiving docetaxel monotherapy after an immunotherapy are anticipated to be alive after 5 years. Survival projections from the expert clinicians after 5, 10, 20 and 25 years for pre-treated *RET* fusion-positive patients receiving docetaxel monotherapy were consistently substantially lower than the predictions informed by the stratified lognormal docetaxel curve applied using the Company's original evidence synthesis methods and survival analyses, and in the Company's revised analyses and model.[1] In addition, the ERG's prediction that [redacted] (Company's original model), or [redacted] (Company's revised model) of patients receiving docetaxel monotherapy would be alive after 25 years is not plausible, as it is unlikely any patients with metastatic disease would reach age 84 (as per the starting age of 59.4 years in the base case analysis). Expert clinician feedback therefore suggests that the ERG's survival estimates for patients treated with docetaxel monotherapy in the second line are an overestimation and unrealistic for this patient population. Since the QALY increment for nintedanib plus docetaxel is added to this overestimated docetaxel arm, the ERG's estimate of [redacted] months mean OS for the nintedanib plus docetaxel arm using the Company's original model is also anticipated to be a significant overestimation. It is further noted that the QALY gain added for nintedanib plus docetaxel was sourced from a cost-effectiveness analysis for a broad population of advanced NSCLC patients, and therefore does not consider any prognostic factors influencing survival associated with the presence of a *RET* gene fusion. With regards to the clinician estimates for selpercatinib, a published median OS estimate of 49.3 months has been reported in *RET* fusion-positive patients receiving selective *RET* tyrosine kinase inhibitors, which could suggest that the clinicians 5-year survival estimates may be pessimistic, although estimates were from a small population (n=60) and using a retrospective study design.[20]

		Table 5. Survival projections for previously treated patients receiving docetaxel monotherapy or selpercatinib

Population	5-year survival (%)	10-year survival (%)	20-year survival (%)	25 year-survival (%)
ERG model predictions using Company's original model[a]				
RET fusion-positive patient receiving docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
ERG model predictions using Company's revised model[b]				
RET fusion-positive patient receiving docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Clinical expert one				
Patient receiving docetaxel monotherapy after prior immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving docetaxel monotherapy after immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving selpercatinib[c]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical expert two				
Patient receiving docetaxel monotherapy after prior immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving docetaxel monotherapy after immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving selpercatinib[c]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Docetaxel survival projections using the stratified lognormal extrapolation for docetaxel monotherapy used in the originally submitted Company cost-effectiveness model. [b] Docetaxel survival projections using the stratified lognormal extrapolation for docetaxel monotherapy used in the revised Company cost-effectiveness model for technical engagement. [c]both clinical experts were hesitant to give reliable prediction beyond 5 years due to lack of long-term data for *RET*-targeted therapies in NSCLC, therefore, predictions for selpercatinib beyond 5 or 10 years are uncertain and listed as unknown.
Abbreviations: ERG: Evidence Review Group; *RET*: rearranged during transfection.

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Revised survival extrapolations

Given the revisions to the NMA approach to produce more reliable survival estimates in the *RET* fusion-positive NSCLC population (see the response to Issue 6), it was necessary to generate an updated set of survival extrapolations for selpercatinib and docetaxel monotherapy. PFS and OS functions for the other relevant comparator (nintedanib plus docetaxel) were constructed through the application of the hazard ratio generated in the revised NMA to the reference (docetaxel) arm extrapolation (Table 6). For the selpercatinib arm, as IPD were available to inform long-term extrapolations for PFS, it was not necessary to apply a hazard ratio to the reference arm to generate these.

Table 6. Hazard ratios (95% CrI) applied to reference arm (FE hierarchical exchangeable)

Drug (patient subgroup)	PFS	OS
Docetaxel monotherapy	NA	NA
Nintedanib + docetaxel	[redacted]	[redacted]

Abbreviations: CrI: credible interval; FE: fixed effects; NA: not applicable: OS: overall survival; PFS: progression-free survival

Progression-free survival

Model fit statistics for the parametric survival functions are available below in Table 7 and long-term extrapolations for PFS are available in Appendix G, Figure 15 and Figure 16. Among all the curves explored, minimal difference between the AIC and BIC statistics was observed, although the best fitting curve, as indicated by both the AIC and BIC statistics, was the unstratified Gamma.

Table 7. Model fit statistics for PFS second line parametric survival functions for selpercatinib and reference arm

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Unstratified				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified				
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

All the selected curves presented to the clinical experts produced consistent predicted medians for selpercatinib (range [redacted] months), except for the stratified lognormal. The experts indicated that for *RET* fusion-positive patients treated with either selpercatinib or docetaxel, many of the curves were predicting over-optimistic estimations of long-term PFS. Curves that produce longer tails, as seen with immunotherapies, would not be seen with targeted therapies such as selpercatinib. In this respect, the Gompertz (stratified or unstratified) were deemed the most realistic curves; the stratified curve was ultimately selected to account for proportional hazards violation observed in the PFS NMA and the need to apply a hazard ratio to generate the PFS estimate for nintedanib plus docetaxel. The stratified Gompertz produced consistent predictions to the observed trial data from LIBRETTO-001 (predicted = [redacted] months vs observed = [redacted] months) but generated a smaller tail and only a small % remaining progression-free after 5 years.

The revised Company base case extrapolations for selpercatinib and comparators for PFS is presented in Figure 3. As the best fitting curve according to goodness-of-fit statistics, the unstratified Gamma function is applied in a scenario analysis.

Figure 3. Revised Company base case extrapolations for selpercatinib and comparators for PFS, stratified Gompertz

[redacted]

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

Overall survival

Model fit statistics for the parametric survival functions are provided in Table 8, and long-term extrapolations for OS are available in Appendix G, Figure 17 and Figure 18. Among all the curves explored, minimal difference between the AIC and BIC statistics was observed, although the best fitting curve, as indicated by both the AIC and BIC statistics, was the exponential and Weibull as the second best fitting curve.

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		Table 8. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm

Table 8. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Unstratified				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified				
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Feedback from the clinical experts suggested that the adjustment made to the docetaxel reference arm, through application of the time acceleration factor and propensity score matching using multivariable regression, had resulted in overly optimistic estimations for OS. Both experts estimated that approximately [redacted] of *RET* fusion-positive patients receiving docetaxel would be alive after 5 years, [redacted] after 10 years and [redacted] after 25 years (Table 5). As a result, an overly optimistic prediction for OS in nintedanib plus docetaxel was also anticipated, following the application of the hazard ratio from the NMA.

Clinical expert feedback suggested that the most plausible extrapolations for OS for both arms was achieved using the stratified Gamma, stratified Weibull or Spline/Knot=1 survival function. An illustration of the predicted survival rates produced from a selection of curves presented to the experts are shown in Table 9 below.

Table 9. Long-term predicted survival estimates with the Stratified Weibull, Spline/Knot=1 and Stratified Gamma

	Median PFS[a] (months)	Median OS (months)	5-year	10-year	25-year
Exponential					
Docetaxel	5.54	21.23	14.0%	1.97%	0%
Selpercatinib	[redacted]	[redacted]	45.6%	20.86%	2.0%
Weibull					
Docetaxel	5.54	20.77	10.0%	0.66%	0.0%
Selpercatinib	[redacted]	[redacted]	39.0%	12.83%	0.3%
Loglogistic					
Docetaxel	5.54	21.00	20.5%	9.60%	3.1%
Selpercatinib	[redacted]	[redacted]	43.5%	24.03%	8.6%
Gompertz					
Docetaxel	5.54	21.00	5.1%	0.0%	0.0%
Selpercatinib	[redacted]	[redacted]	29.3%	0.79%	0.0%
Gamma					
Docetaxel	5.54	20.07	11.1%	1.04%	0.0%
Selpercatinib	[redacted]	[redacted]	39.8%	14.30%	0.6%
Stratified loglogistic					
Docetaxel	5.54	21.00	20.1%	9.26%	2.9%
Selpercatinib	[redacted]	[redacted]	45.4%	26.09%	9.8%
Stratified Weibull					

Docetaxel	5.54	20.77	10.5%	0.78%	0.0%
Selpercatinib	[redacted]	[redacted]	36.1%	9.99%	0.1%
Spline/Knot 1					
Docetaxel	5.54	20.77	9.0%	0.5%	0.0%
Selpercatinib	[redacted]	[redacted]	37.2%	10.9%	0.2%
Stratified Gamma					
Docetaxel	5.54	20.77	11.2%	1.06%	0.0%
Selpercatinib	[redacted]	[redacted]	39.3%	13.83%	0.5%

Footnotes: [a]fixed by applying the stratified Gompertz.
Abbreviations: OS: overall survival; PFS: progression-free survival.

The predicted survival rates at 5-,10- and 25-years were similar for both selpercatinib and docetaxel for stratified Weibull, Spline/Knot=1 and stratified Gamma, and produced consistent long-term predictions at 10- and 25-years compared to those provided by the clinical experts in Table 4. For the Spline/Knot=1, 10-year survival was predicted by the model at [redacted] and [redacted] for selpercatinib and docetaxel, respectively, compared to [redacted] and [redacted] estimated by the clinical experts for selpercatinib and docetaxel, respectively. In contrast, more conservative curves such as the Gompertz predicted a 5-year survival for selpercatinib ([redacted]) that was more consistent with estimates provided by clinical experts ([redacted]), compared to the stratified Weibull ([redacted]), Spline/Knot=1 ([redacted]) and stratified Gamma ([redacted]), but much lower 10-year survival rates at [redacted] and [redacted] for selpercatinib and docetaxel, respectively, compared to those estimated by the clinical experts. As such, the stratified Weibull, Spline/Knot=1 and stratified Gamma were considered to, overall, provide a more clinically plausible OS estimate than the more conservative Gompertz.

The stratified Weibull was the most conservative option and stratified Gamma most optimistic out of the three curves preferred by the experts. Consequently, the Spline/Knot=1 function was applied due to the application of hazard ratios and assumption of proportional hazards for nintedanib and docetaxel to docetaxel, and as it produced an extrapolation in-between the stratified Weibull and stratified Gamma distributions. Although spline-based models may not have a theoretical distribution, they can be used to fit survival curves where several 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 log-normal distributions may exist within the data. Accordingly, the use of spline-based models is a relatively simple method of modelling complex survival data, and when only the intercept of a spline-based model varies by treatment, this provides a proportional hazards model (thus making it acceptable for a treatment effect hazard ratio to be applied).

The recommended base case extrapolations for selpercatinib and comparators for OS is presented in Figure 4.

Figure 4. Base case extrapolations for selpercatinib and comparators for OS, Spline/Knot=1

[redacted]

Abbreviations: KM: Kaplan-Meier; OS: overall survival.[redacted]

		Scenario analyses Scenario analyses for PFS included using the unstratified Gamma, Gompertz, stratified Weibull and Spline/Knot=1. Scenario analyses for OS included the unstratified exponential and Weibull as the two best fitting distibutions, and stratified Weibull and stratified Gamma as alternaitve clinical expert choices. Results from the scenario analyses are presented in Appendix J.
Key issue 9: Progressive disease health state utility value	YES	Eli Lilly and Company acknowledge the ERG's preference to use the health state utility value (HSUV) for progressed disease (PD), which was chosen by the NICE Committee during assessment of TA484 (0.569).[21] As outlined in the Company's original submission (Document B, Section B.3.4.1), European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 data were collected in the LIBRETTO-001 study. The questionnaire was to be answered by the patient to the best of his/her ability within 7 days of each radiologic assessment, preferably prior to learning the results of the radiologic disease assessment, and at the end of the treatment visit (approximately every 8 weeks).[5] Utility was estimated from the EORTC QLQ-C30 data using mapping algorithms reported by Khan et al. (2016).[22] As outlined in the Company's original submission (Document B, Section B.3.4.2), the beta-binomial and RE linear regression models, provided in the mapping study by Khan et al. (2016),[22] were found to offer the best fit to the data, but produced unrealistic baseline utility values (0.9984 and 0.99, respectively). As such, an additional mapping algorithm reported by Young et al. (2015)[23] that maps the EORTC QLQ-C30 to the 3-level EuroQol 5-dimensions questionnaire (EQ-5D-3L) has since been explored. The utility estimates from TA484 (Company original base case and ERG preference) and the new mapping algorithm from Young et al. (2015)[23] are summarised in Table 10.

		Table 10. Utility estimates for pre-treated NSCLC

Table 10. Utility estimates for pre-treated NSCLC

Health State	Company Base Case for Original Submission	ERG Preference	LIBRETTO-001 EORTC data mapped to EQ-5D-3L
			Young (2015)[a]
PF	0.713[b]	0.713[c]	[redacted]
PD	0.688[d]	0.569[e]	[redacted]

Footnotes: [a] Using response mapping; [b] ERG preferred estimate in TA484 (Guidance section 4.18; Committee Papers P 550) based on van den Hout 2006 and EQ-5D data collected in CheckMate 057; [c] All post-baseline pre-progression assessments; [d] Manufacturers estimate in TA484; [e] The original HSUV of 0.688 used by the manufacturer was considered too optimistic by the ERG.

Abbreviations: CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-3L: 3-level EuroQol five-dimensions questionnaire; ERG: Evidence Review Group; NR: not reported; NSCLC: non-small cell lung cancer; PD: progressed disease; PF: progression-free; SD: standard deviation; SE: standard error; TA: technology assessment.

Source: TA484[21] and Eli Lilly and Company Data on File 2020.[5]

The mapping algorithm from the Young et al (2015)[23] study produced a plausible utility value for the progression-free (PF) health state of [redacted] Use of this value would adhere more closely with NICE's reference case[24] compared with values from TA484, as it was derived in patients with advanced non-squamous *RET* fusion-positive NSCLC (i.e. the target population), as opposed to advanced NSCLC patients without a *RET* fusion.[21] Consequently, a utility value of [redacted] was used for the PF health state in the Company's revised base case economic model. Alternative utility values were considered as scenario analyses.

The PD health state utility value estimated using the Young et al (2015)[23] mapping algorithm was [redacted]. The Young et al. (2015)[23] PD value exceeded both the utility value used in the Company's original submission (0.688) and the ERG's preferred value (0.569), which were both derived from TA484. The Young et al. mapped utility value of [redacted] may be considered less plausible due to the low number of EORTC QLQ-C30 observations for PD collected from LIBRETTO-001 thus far. However, because advanced NSCLC patients with a *RET* fusion tend to be younger and non-smokers,[6] the Company consider that these patients likely have a higher utility value than the general population of advanced NSCLC patients, which may partially explain the higher PD value obtained from the mapping algorithms.

		Given the low patient numbers informing the mapping process for PD, [redacted] was not chosen as the revised value to inform the updated base case analyses. Instead, the mid-point between the ERG's preferred value and the value chosen in the Company's original submission was therefore selected for the PD health state in the Company's revised base case economic model (i.e. 0.628). The revised results of Company's cost-effectiveness analysis are presented in Appendix J.
Key issue 10: Costing of treatment with selpercatinib	YES	Eli Lilly and Company agree with the ERG that patients with PD could continue to receive selpercatinib beyond progression in clinical practice if their clinician deems that they are continuing to derive clinical benefit.[1] Accordingly, in order to capture this, the cost-effectiveness model has been updated with a revised, conservative approach to modelling time-to-treatment discontinuation (TTD). In the updated base case analysis, time on treatment curves were based on PFS, but were adjusted such that patients were assumed to discontinue treatment in the model eight weeks after a PFS event. This was informed by the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial ([redacted] days [IAS]) (Table 11). Treatment discontinuation for comparators was modelled to align with PFS, capped at a maximum number of cycles where specified. The updated cost-effectiveness results are presented in Appendix A.

Table 11. Mean time (days) between meeting the PFS endpoint and treatment discontinuation for NSCLC pre-patients in LIBRETTO-001

	Pre-treated NSCLC (IAS) (N=184)
Discontinued treatment during trial follow-up, n (%)	[redacted]
Time between PFS and treatment discontinuation	
Mean (days)	[redacted]
SD	[redacted]
Min, max (days)	[redacted]
95% CI	[redacted]

Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progression-free survival; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Key issue 11: Cost of testing for *RET* fusions	YES	It is likely that next generation sequencing (NGS) at genetic hubs will become the routine method for conducting molecular genetic testing in the NHS. The use of NGS to identify *RET* gene fusions is considered to be cost-effective, as it allows multiple potentially oncogenic genes to be tested for abnormalities in parallel. Since this approach will be routinely implemented across the UK, Eli Lilly and Company believe that the cost of screening a population of pre-treated non-squamous NSCLC patients for *RET* fusions, to identify which patients will receive selpercatinib, should theoretically not be included in the economic assessment. However, the Company recognise that it is uncertain when NGS within these hubs will be fully operational and a cost specifically attributed to the *RET*-fusion portion of a multi-gene testing NGS panel has therefore been applied in the updated model. A figure of [redacted] per test was recommended by NHS England. This figure is based on a prevalence rate for *RET* fusions among NSCLC patients of 1.5% (Sireci et al. 2019),[25] which equates to approximately [redacted] [redacted]/0.015) per *RET* fusion-positive patient identified. This value has been applied in the model. Eli Lilly and Company believe this cost to represent a suitable proxy for testing *RET* among multiple genetic markers in the UK via the genetic hub structure. The updated cost-effectiveness results, which account for the costs associated with *RET* testing, are presented in Appendix A.
Key issue 12: NICE End of Life criteria may not be met **Questions for clinical experts:** What is the expected mean survival of people with RET fusion-positive advanced NSCLC receiving second-line chemotherapy	YES	As outlined in the Company's response to Issue 8, the mean OS estimate for patients receiving nintedanib plus docetaxel of [redacted], produced using the ERG's preferred modelling methods, is considered to be a substantial overestimate of survival on this treatment. Expert clinical opinion was that patients receiving docetaxel monotherapy alone in the second line would be unlikely to survive for more than 24 months, and survival estimates for docetaxel monotherapy using the ERG's preferred modelling methods were much greater than estimates provided by the expert clinicians. Since the QALY increment for nintedanib plus docetaxel is added to this overestimated docetaxel arm, the ERG's estimate for the nintedanib plus docetaxel arm is also anticipated to be a significant overestimation.[1] The Company's original survival estimate for nintedanib plus docetaxel (median OS: [redacted] months) and the Company's revised survival estimate ([redacted] months) are similarly considered to be overestimations. As discussed in response to Issue 6, the application of the time acceleration factor to adjust for *RET* fusion status, in addition to use of multivariable regression and propensity score matching to adjust for

<table>
<tr>
<td>(docetaxel with or without nintadenib)?

Is it plausible that selpercatinib will increase the survival of people with RET fusion-positive advanced NSCLC by at least 3 months compared with docetaxel with or without nintadenib?</td>
<td></td>
<td>
other prognostic factors, resulted in overestimates for OS for the reference arm, and thus nintedanib plus docetaxel, for which hazard ratios from the NMAs were applied.

The Company's revised base case survival outcomes are summarised in Table 12.

Table 12. Revised base case clinical outcomes: PFS and OS
<table>
<tr><th>Intervention/comparator</th><th>Median PFS (months)</th><th>Median OS (months)</th></tr>
<tr><td>Selpercatinib</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Docetaxel monotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Nintedanib + docetaxel</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: OS: overall survival; PFS: progression-free survival.

Given the above, RET fusion-positive patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second line in the UK are anticipated to have a life expectancy of <24 months and are highly likely to experience an extension to life >3 months if they were to receive selpercatinib monotherapy. Evidence to support the consideration of selpercatinib under the End of Life are summarised in Table 13.

Table 13. End-of-life criteria
<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Yes – The results of the base case cost-effectiveness analysis (Appendix J) demonstrated that nintedanib plus docetaxel had a predicted survival of [redacted] months and docetaxel monotherapy a predicted survival of [redacted] months.
However, as described in Issue 6, the adjustment made to the docetaxel reference arm, through application of the time acceleration factor to adjust for RET fusion-positive status and propensity score matching, had resulted in overly optimistic OS estimations for both comparators. The median OS of [redacted] months and [redacted] months for nintedanib plus docetaxel and</td></tr>
</table>
</td>
</tr>
</table>

			docetaxel monotherapy, respectively, are therefore considered to be overestimations.
		2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally at least an additional 3 months, compared with current NHS treatment	**Yes** – Base case cost-effectiveness results illustrate that selpercatinib is associated with an increase in survival of [redacted] months and [redacted] months compared to docetaxel and nintedanib plus docetaxel, respectively. This [redacted] emphasises the survival benefit of selpercatinib compared with current NHS treatment and exceeds the 3-month additional survival target.

Abbreviations: NHS: National Health Service; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

Targeted literature review: *RET* fusion-positive NSCLC studies

To supplement estimates of likely survival for comparators relevant to selpercatinib, a targeted literature review was conducted to identify studies assessing the efficacy of treatments in advanced *RET* fusion-positive NSCLC (Appendix H, Table 27). Results from the REVEL trial[17] and the LUME-Lung 1 trial[26] in non-*RET* fusion positive patients are also included in Table 27 for reference.

No studies that assessed the efficacy of relevant comparators to selpercatinib in the UK in pre-treated advanced non-squamous *RET* fusion-positive NSCLC patients were identified. As a result of this, Eli Lilly and Company reviewed the only identified study in *RET* fusion-positive patients assessing treatment in a second line population (Drilon 2016).[27] In Drilon 2016, median survival in advanced *RET* fusion-positive NSCLC patients treated in the second line and beyond with cabozantinib was 9.0 months. This is significantly lower than Company cost-effectiveness model estimates for either docetaxel monotherapy ([redacted] months) or nintedanib plus docetaxel ([redacted] months).[27] Although cabozantinib is not a comparator relevant to the UK, these results show that treatment of advanced *RET* fusion-positive patients with a broad-acting MKI, similar to nintedanib, results in a survival estimate well under two years.

Further evidence in advanced *RET* fusion-positive patients was identified in a mixture of first- and second-line patients in Shen 2020.[28] Shen 2020 reported a median OS of 22.6 months in 10 advanced *RET* fusion-positive NSCLC patients that had never received pemetrexed-based chemotherapy, and 35.2 months in 28 patients that had received pemetrexed-based chemotherapy.[28] Although estimates for

		patients that had received pemetrexed-based chemotherapy exceeded two years, OS was measured from the date of confirmed Stage IIIa/IV disease, which prolonged survival estimates compared with Company estimates.[28] In addition, the study was completed in China, which has different treatment patterns and patient characteristics to the UK.[28] Further evidence in advanced *RET* fusion-positive patients was identified in a population of first line patients.[29] Gautschi 2017 reported a median OS of 24.8 months in 70 *RET* fusion-positive NSCLC patients treated with platinum-based chemotherapy and 23.6 months in 57 *RET* fusion-positive patients treated with pemetrexed plus a platinum agent.[29] If estimates of survival for first-line non-targeted therapy in *RET* fusion-positive patients are close to or less than 24 months, it is deemed highly unlikely that survival in second line with non-targeted therapies such as docetaxel and nintedanib plus docetaxel would be greater than 24 months. This again would suggest that the estimated median OS from the Company's cost-effectiveness model (as well as the ERG's estimates) for patients receiving docetaxel monotherapy and nintedanib plus docetaxel in the second line is an overestimation. Finally, median OS trial data for non-*RET* fusion positive patients receiving docetaxel monotherapy (REVEL: 9.1 months)[17] and nintedanib plus docetaxel (LUME-Lung 1: 12.6 months)[26] is also significantly less than 24 months. Although positive *RET* fusion status has been associated with favourable OS compared with patients without a *RET* fusion,[18] it is considered highly unlikely that this would extend life beyond 24 months for either treatment. Furthermore, even with the highly optimistic estimations from the Company model for the comparators, there is still a survival benefit of greater than 3-months between selpercatinib and relevant UK comparators. Given the above analysis, Eli Lilly and Company believe that: • The ERG's 5-year survival projection of [redacted] (original Company model), or [redacted] (revised Company model) for pre-treated advanced non-squamous and *RET* fusion-positive NSCLC patients treated with docetaxel monotherapy does not align with expert clinical opinion and is likely to be highly optimistic. As such, the ERG's mean OS estimate of [redacted] using the Company's original model for patients treated with nintedanib plus docetaxel is likely to be an overestimate and does not align with expert clinical opinion or the published literature. Furthermore, this estimate converges with the Company mean life-year estimate predicted by the model for

		selpercatinib [redacted], which is not considered to be clinically plausible, given the treatment effects estimated by the Company's revised NMA and that selpercatinib specifically targets the oncogenic driver of the patient's cancer. • The Company considers that its cost-effectiveness model OS estimates for comparators to selpercatinib are more accurate than the ERG's, but likely remain overly optimistic when compared with expert clinical opinion and considering published survival outcomes for the advanced *RET* fusion-positive patients receiving non-targeted therapies in the first line and second line setting • Pre-treated advanced *RET* fusion-positive NSCLC patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second line in the UK have a life expectancy of <24 months and are highly likely to experience an extension to life >3 months if they were to receive selpercatinib monotherapy, therefore meeting both end-of-life criteria
Key issue 13: Absence of data for subgroups of patients listed in the final scope issued by NICE **Question for clinical experts:** Do you agree with company positioning of selpercatinib in non-squamous disease?	NO	Eli Lilly and Company agree with the clinical advice provided to the ERG that it was reasonable to exclude patients with advanced squamous cell NSCLC, because *RET* fusions are extremely rare in this population.[6]

Appendix A

Summary of changes to the company's cost-effectiveness estimate(s)

Following feedback from the ERG, Eli Lilly and Company have updated the economic model to produce a revised base case. The revised cost-effectiveness model, fully annotated to highlight updates made since the original submission, is provided alongside this document. A summary of the updates made to inform the revised base case of the model is presented in Table 14 below. Please note that given the short timeframe associated with the Technical Engagement and the significant updates required to the economic model, it was not possible for Eli Lilly and Company to provide updated base case ICERs for each change made to the economic model.

The LIBRETTO-001 data from the 30th March 2020 data cut off, presented in response to Issue 2, represent a larger sample size and longer duration of follow up. As illustrated in the response to Issue 2, similar results were observed for PFS and OS between the 30th March 2020 and 16th December 2019 data cut. Whilst these data corroborate and therefore provide additional confidence in the results of the 16th December 2019 data cut, they have not been used to conduct the ITC, nor to inform the revised base case economic model, due to time constraints and as only a small number of additional events had occurred by the later data cut. For the reasons described above, these data would have minimal impact on the cost-effectiveness results.

A summary of the results from the revised base case model are available in Table 15. Full updated model results are available in Appendix J.

Table 14. Summary of changes to the revised base case cost-effectiveness model

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement
Key issue 4: Relevant comparator treatments	All patients: • Nintedanib + docetaxel • Atezolizumab PD-L1≥1%: • Nivolumab • Pembrolizumab	All patients: • Nintedanib + docetaxel • Docetaxel monotherapy
Key issue 5: The relevance of populations participating in the trials that provided comparator evidence for the company NMAs	NMA model selection (PFS and OS): Fixed effects hierarchical exchangeable model adjusted for age (centered on 61 years of age)	NMA model selection (PFS and OS): Fixed effects hierarchical exchangeable model

Key issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	Approach to generating and adjusting the pseudo-control arm for LIBRETTO-001: • Adjust REVEL IPD for prognostic impact of *RET* fusion-positive status using Flatiron data • Adjustment for further prognostic factors using TMLE	Approach to generating and adjusting the pseudo-control arm for LIBRETTO-001: • Adjust REVEL IPD for prognostic impact of *RET* fusion-positive status using Flatiron data • Adjustment for further prognostic factors using propensity score matching
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Key issue 8:** The company modelling of survival for patients receiving nintedanib + docetaxel	PFS extrapolation: Stratified gamma	PFS extrapolation: Stratified Gompertz (updated based on revised NMA approach and further clinical input)
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Key issue 8:** The company modelling of survival for patients receiving nintedanib + docetaxel	OS extrapolation: Unstratified exponential	OS extrapolation: Spline/Knot=1 (updated based on revised NMA approach and further clinical input)
Key issue 9: Progressed disease health state utility value	PF: 0.713 (TA484)[21] PD: 0.688 (TA484)[21]	PF: [redacted] (LIBRETTO-001; EORTC-QLQ-C30 mapped to EQ-5D-3L using Young et al [2015])[23] PD: 0.628 (intermediate between the ERG preferred value [0.569] and the company's original PD utility value [0.688])
Key issue 10: Costing of treatment with selpercatinib	Time to treatment discontinuation: assumed TTD was equivalent to PFS	Time to treatment discontinuation: TTD curves were based on PFS but the selpercatinib TTD curve was shifted to account for the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial
Key issue 11: Cost of testing for *RET* fusions	The cost of *RET* testing not included	Cost specifically attributed to the *RET*-fusion portion of a multi-gene testing NGS panel included in the model
Additional change 1	No PAS applied	A simple PAS, representing a [redacted] discount, has been approved for selpercatinib by PASLU and has been applied to the model Further details are available in Appendix

Additional change 2	Selpercatinib acquisition costs: List price of a 60-capsule bottle of 80 mg or 40 mg: £[redacted]	Selpercatinib acquisition costs: List price 60 capsule bottle of 80 mg: £4,680.00 60 capsule bottle and 40 mg: £2,340.00 Selpercatinib acquisition costs: Price (with proposed PAS discount applied) 60 capsule bottle of 80 mg: £[redacted] 60 capsule bottle and 40 mg: £[redacted] Further details are available in Appendix I
Additional change 3	ECG costs: ECG costs applied to intervention and comparators in health state costs	ECG costs: One-off cost of seven ECGs is included in the model for selpercatinib only based on final SmPC[30] Further details are available in Appendix I
Additional change 4	Selpercatinib dose reductions: The mean dose intensity in the LIBRETTO-001 trial ([redacted]) was used to account for dose reductions and any treatment breaks	Selpercatinib dose reductions: Proportions of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the LIBRETTO-001 trial Further details are available in Appendix I

Abbreviations: FE: fixed effects; IPD: individual patient data; ECG: electrocardiogram; NGS: next-generation sequencing; NMA: network meta-analysis; OS: overall survival; PAS: patient access scheme; PASLU: patient access scheme liaison unit; PD-L1: programmed death ligand 1; PFS: progression-free survival; *RET*: rearranged during transfection: SmPC: Summary of Product Characteristics; TMLE: targeted minimum loss-based estimation; TTD: time-to-treatment discontinuation.

Updated base case cost-effectiveness results

Table 15. Revised base case cost-effectiveness model results for *RET* fusion-positive NSCLC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)

Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,833
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	104,016[a]	69,411
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,833	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-year.

Appendix B

Issue 2: LIBRETTO-001 Trial Survival Events and Length of Follow-Up

Efficacy data from 30th March 2020

Efficacy data for the entire IAS efficacy population (N=218) as of the 30th March 2020 are presented in full below.

ORR by RECIST v1.1 (primary endpoint)

Table 16. BOR, ORR and CBR by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

Status	**IAS N=218**
BOR (n, %)[a]	
CR	9 (4.1)
PR	115 (52.8)
SD	81 (37.2)
SD*,[b]	60 (27.5)
PD	5 (2.3)
NE	8 (3.7)
ORR (CR+PR)[c,d]	
Number of patients (n, %)	124 (56.9)
95% CI	50.0–63.6
CBR (CR+PR+SD*)[d,e]	
Number of patients (n, %)	184 (84.4)
95% CI	78.9–89.0

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] stable disease lasting 16 weeks or more; [c] objective response rate is defined as the proportion of patients with best overall response of confirmed CR or PR; [d] 95% confidence intervals calculated using Clopper-Pearson method; [e] Clinical benefit rate is defined as the proportion of patients with best overall response of confirmed CR, PR or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of selpercatinib until the criteria for disease progression was first met.
Abbreviations: BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; NE: not estimable; NSCLC: non-small cell lung cancer; ORR: objective response rate; PD: progressive disease; PR: partial response; *RET:* rearranged during transfection; SD: stable disease.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

DOR (secondary endpoint)

Table 17. DOR by IRC with confirmed CR or PR for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

Status	IAS N=218
Patients with best response of confirmed CR or PR[a]	124
Response states (n, %)[b]	
Disease progression	34 (27.4)
Died (no disease progression beforehand)	4 (3.2)
Censored	86 (69.4)
Reason censored (n, %)	
Alive without documented disease progression	83 (66.9)
Subsequent anti-cancer therapy of cancer related surgery without documented PD	3 (2.4)
Duration of response (n, %)	
<6 months	36 (29.0)
≥6 to 12 months	51 (41.4)
≥12 to 18 months	29 (23.4)
≥18 to 24 months	5 (4.0)
≥24 months	3 (2.4)
Duration of response (months)[c,d]	
Median	17.51
95% CI	12.1–NE
Minimum, maximum	1.8+, 29.8+
Duration of follow-up (months)[c]	
Median	11.99
25th, 75th percentiles	7.4, 15.9
Rate (%) of DOR[c,e]	
6 months or more	85.8
95% CI	77.9, 91.1
12 months or more	69.1
95% CI	58.1, 77.8

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] Status as of the patients last disease assessment on or before cut-off date; [c] Estimated based on Kaplan-Meier methods. NE = not estimable/ + = censored observation; [d] 95% confidence interval was calculated using Brookmeyer and Crowley method; [e] 95% confidence interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; CR: complete response; DOR: duration of response; IAS: Integrated Analysis Set; IRC: independent review committee; PAS: Primary Analysis Set; NE: not estimable; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

PFS (secondary endpoint)

Table 18. PFS by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

	IAS N=218
Status (n, %)[a]	
Disease progression	74 (33.9)
Censored	144 (66.1)
Duration of PFS (months)[b]	
Median	19.29
95% CI	16.5–NE
Minimum, maximum	0.0+, 30.6+
Duration of follow-up (months)	
Median	13.60
25th, 75th percentiles	9.0, 16.6
Rate (%) of PFS[b,c]	
6 months or more	84.4
95% CI	78.7–88.7
12 months or more	69.7
95% CI	62.2–75.9
18 months or more	54.2
95% CI	44.4–63.1
24 months or more	43.7
95% CI	31.5–55.4

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] Estimated based on Kaplan-Meier methods. NE = not estimable/ + = censored observation; [c] 95% confidence interval was calculated using Brookmeyer and Crowley method.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: independent review committee; NE: not estimable; NSCLC: non-small cell lung cancer; PAS: Primary Analysis Set; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

Figure 5. Kaplan-Meier plot of PFS for second line (IAS) *RET*-fusion positive NSCLC patients (30th March 2020 data cut; IRC)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; IRC: Independent Review Committee; NSCLC: non-small cell lung cancer; PFS: progression-free survival; *RET*: rearranged during transfection.

OS (secondary endpoint)

Table 19. OS by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

	IAS N=218
Status (n, %)[a]	
Died	41 (18.8)
Censored	177 (81.2)
Duration of OS (months)[b,c]	
Median	NE
95% CI	25.7–NE
Minimum, maximum	0.3, 34.5+
Duration of follow-up (months)	
Median	14.26
25th, 75th percentile	10.1, 19.5
Rate (%) of OS[b,c]	
6 months or more	95.4
95% CI	91.6–97.5
12 months or more	88.1
95% CI	82.5–91.9
18 months or more	77.6
95% CI	69.4–83.9
24 months or more	67.3
95% CI	55.4–76.7

Footnotes: [a] Status as of the last contact on or before the 30th March 2020; [b] Estimate based on Kaplan-Meier method. NE = not estimable/ + = censored observation; [c] 95% confidence interval was calculated using Brookmeyer and Crowley method.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: independent review committee; NE: not estimable; NSCLC: non-small cell lung cancer; OS: overall survival; PAS: Primary Analysis Set; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

Figure 6. Kaplan-Meier plot of OS for second line (IAS) *RET*-fusion positive NSCLC patients (30th March 2020 data cut; IRC)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; IRC: Independent Review Committee; NA: not applicable; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

Appendix C

Issue 3: Prior Treatments Received by the LIBRETTO-001 Trial Population Do Not Reflect NHS Clinical Practice

Breakdown of prior treatments in LIBRETTO-001

A detailed breakdown of the prior treatments received by patients in the IAS analysis set is presented in Table 20. Kaplan-Meier plots of PFS and OS for the IAS MKI-naïve subgroup are provided below in Figure 7 and Figure 8, respectively.

Table 20. Prior treatments received by the IAS analysis set in LIBRETTO-00

Characteristic	IAS N=184
Received prior systemic therapy n (%)	
Yes	184 (100.0)
No	0 (0.0)
Prior systemic regimens n (%)	
0	0 (0.0)
1-2	100 (54.3)
3 or more	84 (45.7)
Number of prior systemic regimens n	
Mean (SD)	[redacted]
Median (range)	[redacted]
Type of prior systemic therapy n (%)	
MKI	67 (36.4)
Cabozantinib	[redacted]
Vandetanib	[redacted]
Sorafenib	[redacted]
Lenvatinib	[redacted]
Other MKIs	[redacted]
Chemotherapy	184 (100.0)
Platinum Chemotherapy	184 (100.0)
Radioactive Iodine	[redacted]
Anti-PD1/PD-L1 Therapy	100 (54.3)
Selective *RET* Inhibitor	[redacted]
Taxane Chemotherapy	[redacted]
Other Systemic Therapy	[redacted]

Footnotes: Patients may be counted in more than one row of type of prior systemic therapy. 16th December 2019 data-cut

Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; PD1: programmed cell death protein 1; PD-L1: programmed death ligand 1; *RET*: rearranged during transfection; SD: standard deviation.

Figure 7. Kaplan-Meier plot of PFS by Independent Assessor for second line (IAS) *RET*-fusion positive NSCLC patients without prior MKI treatment (30th March 2020 data cut)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; NSCLC: non-small cell lung cancer; PFS: progression-free survival; *RET*: rearranged during transfection.

Figure 8. Kaplan-Meier plot of OS by Independent Assessor for second line (IAS) *RET*-fusion positive NSCLC patients without prior MKI treatment (30th March 2020 data cut)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; NA: not applicable; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

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Appendix D

Issue 5: Relevance of the population participating in the trials that provided comparator evidence for the Company NMAs

The DIC values for key covariates informing the NMA meta-regression are provided in Table 21.

Table 21. DIC statistics for OS, PFS and ORR based on either fixed or random effects models with individual covariates

Covariate	DIC		
	OS	PFS	ORR
FE – no covariates	[redacted]	[redacted]	[redacted]
RE – no covariates	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model + age	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + age	[redacted]	[redacted]	[redacted]
FE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + ECOG	[redacted]	[redacted]	[redacted]
FE + proportion of male participants	[redacted]	[redacted]	[redacted]
RE + age	[redacted]	[redacted]	[redacted]
RE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
RE + ECOG	[redacted]	[redacted]	[redacted]
RE + proportion of male participants	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion; ECOG: Eastern Cooperative Oncology Group; FE: fixed effects; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RE: random effects.

[a] The hierarchical exchangeable structure was applied only to the model that was found to have the lowest DIC values with covariate adjustments. Hence, the DIC value for fixed effects hierarchical exchangeable model with age is available for OS and PFS while the DIC value for fixed effect hierarchical exchangeable model with Asian participants is available for ORR.

[b] models with convergent issues.

Appendix E

Issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis

Programming language for propensity score matching

The R programme code, used for the Flatiron adjustment for *RET*-status was provided in the original submission (Appendices, Section D.1.8). Code for the propensity score matching approach is provided in Table 22.

Table 22. Programme code used in the propensity score matching

Function	Programme	Code
Estimation of treatment effect		
Pilot *RET* fusion adjusted chart	R	[redacted]
Propensity score matching	R	[redacted]

		[redacted]

		[redacted]
Propensity score matching using a generalised boosted model	R	[redacted]

		[redacted]

		[redacted]

Code for NMA of English second line treatments

OPENBUGS codes were translated into JAGS as the background model code in BATMAN; the programme used to conduct the second line NMA. In this section the JAGS code used in the NMA of English second line treatments for NSCLC are presented.

Figure 9. JAGS code for ORR in the second line NMA (fixed effects plus hierarchical exchange adjusted for the proportion of Asian patients)

[redacted]

Abbreviations: NMA: network meta-analysis; ORR: objective response rate.

Figure 10. JAGS code for PFS in the second line NMA (fixed effects plus hierarchical exchange)

[redacted]

Abbreviations: NMA: network meta-analysis; PFS: progression-free survival.

Figure 11. JAGS code for OS in the second line NMA (fixed effects plus hierarchical exchange)

[redacted]

Abbreviations: NMA: network meta-analysis; OS: overall survival.

Appendix F

Issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis

LIBRETTO-001 and REVEL patient characteristic data pre- and post-adjustment for *RET* fusion status and other prognostic factors

Table 23. Summary of patient characteristics of the REVEL and LIBRETTO pre-treated NSCLC trial populations, before and after adjustment for *RET* fusion status and the propensity score matching process

Characteristic	Baseline characteristics		After *RET* adjustment Before propensity score matching		After propensity score matching[a]
	LIBRETTO-001, IAS (selpercatinib) (N=184)	REVEL (docetaxel + placebo) (N=447)[b]	Selpercatinib arm (N=174)	Docetaxel + placebo arm (N=447)	Docetaxel + placebo arms (N=174)
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology: Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≥ 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis to start of trial (median months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] The analysis followed greedy match as the matching algorithm. [b] A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to generate the pseudo-control arm. [c] The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the need to exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on covariates required for the matching process.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS, Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.

Source: Eli Lilly and Company Ltd. Data on File.(7)

Updated NMA results

The results of the NMA using the propensity score matching approach, which provide comparative efficacy for selpercatinib and relevant comparators in the UK, are reported in the sections that follow. Treatment effects are presented versus the common comparator in the network, docetaxel.

ORR by RECIST v1.1 (primary endpoint)

The relative treatment effects using the FE model (hierarchical exchangeable and adjusted for the proportion of Asian patients) for interventions of interest for ORR versus docetaxel are presented in Table 24 and the forest plot is presented in Figure 12. Relative to nintedanib plus docetaxel, selpercatinib demonstrated higher odds of inducing an ORR compared to docetaxel plus placebo (ORR:[redacted]; 95% CrI: [redacted]).

Table 24. Relative treatment effects expressed as odds ratios versus docetaxel (with 95% CrI) for ORR in second line advanced NSCLC patients

Treatment	Median OR (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Footnotes: [a] Fixed hierarchical exchangeable model adjusted for the proportion of Asian patients.
Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Figure 12. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for ORR in second line advanced NSCLC patients (fixed effects hierarchical exchangeable adjusted for Asian patients)

[redacted]

Abbreviations: CrI: Credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[5]

PFS (secondary endpoint)

The relative treatment effects for interventions of interest for PFS versus docetaxel are presented in Table 25, using the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 13. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of disease progression compared to docetaxel (hazard ratio: [redacted] 95% CrI: [redacted]).

Table 25. Relative treatment effects expressed as hazard ratios versus docetaxel plus placebo (with 95% CrI) for PFS in second line advanced NSCLC patients

Treatment	Median hazard ratio (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Figure 13. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for PFS in second line advanced NSCLC patients (fixed effects hierarchical exchangeable)

[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

OS (secondary endpoint)

The relative treatment effects for interventions of interest for OS versus docetaxel plus placebo are presented in Table 26, for the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 14. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of death compared to docetaxel (hazard ratio: [redacted] 95% CrI: [redacted]).

Table 26. Relative treatment effects expressed as hazard ratios versus docetaxel plus placebo (with 95% CrI) for OS in second line advanced NSCLC patients

Treatment	Median hazard ratio (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Figure 14. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for OS in second line advanced NSCLC patients (fixed effects hierarchical exchangeable)

[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Appendix G

Issues 7 and 8: Survival extrapolations for selpercatinib and comparators

PFS

Long-term extrapolations for PFS are provided below in Figure 15 and Figure 16.

Figure 15. Selpercatinib PFS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

Figure 16. Reference arm (docetaxel) PFS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

OS

Long-term extrapolations for OS are provided below in Figure 17 and Figure 18.

Figure 17. Selpercatinib OS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

Figure 18. Reference arm (docetaxel) OS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

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Appendix H

Issue 12: NICE End of Life Criteria may not be met

The survival estimates from studies assessing the efficacy and effectiveness of treatments in advanced *RET* fusion-positive NSCLC identified in a targeted literature review are presented in Table 27. Results from the REVEL trial[17] and the LUME-Lung 1 trial[26] in non-*RET* fusion positive patients are also included in Table 27 for reference.

Table 27. Summary of survival estimates in advanced[a] NSCLC patients with or without *RET* fusions treated in the first and second line

Treatment (Source)	RWE mOS	Trial mOS	Predicted mOS (model)
Second line non-*RET* fusion positive NSCLC patients			
Docetaxel (REVEL)[17]	-	9.1	-
Nintedanib + docetaxel (LUME-Lung 1)[26]	-	12.6	-
Second line *RET* fusion-positive patients			
Selpercatinib (LIBRETTO-001 [IAS]; N=184 and Company cost-effectiveness model estimate)[5]	-	[redacted]	[redacted]
Docetaxel (Company cost-effectiveness model estimate)[5]	-	-	[redacted]
Nintedanib + docetaxel (Company cost-effectiveness model estimate)[5]	-	-	[redacted]
Cabozantinib (Drilon 2016[a]; 1 prior line; N=12)[27]	-	9.2	-
Cabozantinib (Drilon 2016[a]; >1 prior line; N=7)[27]	-	9.0	-
First line and second line *RET* fusion-positive patients			
Ever received pemetrexed-based chemotherapy (Shen 2020; N=28)[28]	35.2	-	-
Never received pemetrexed-based chemotherapy (Shen 2020; N=10)[28]	22.6	-	-

Received selective *RET* TKI (Tan 2020; N=35)[20]	49.3	-	-
Selective *RET* TKI naïve (Tan 2020; N=25)[20]	15.3	-	-
First line *RET* fusion-positive patients			
Cabozantinib (Drilon 2016[a]; N=6)[27]	NE	-	-
Platinum based chemotherapy (Gautschi 2017; N=70)[29]	24.8	-	-
Pemetrexed + platinum agent (Gautschi 2017; N=57)[29]	23.6	-	-

Footnotes: [a] All studies summarised in Table 27 reported data in advanced (Stages IIIb or IV) NSCLC except Gautschi 2017. In Gautschi 2017, 78% of patients were Stage IV.
Abbreviations: mOS; median overall survival; mPFS: median progression-free survival; NE: not estimable; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; RWE: real world evidence.

Appendix I

Selpercatinib acquisition costs and dose reductions

As noted in Appendix A, the list prices for selpercatinib formulations (60 capsule bottle of 80 mg or 40 mg selpercatinib) have been updated. In addition, a patient access scheme (PAS) has been approved for selpercatinib, representing a simple discount of [redacted] to the list price. Table 28 presents the drug acquisition costs for selpercatinib based on its current PAS price, licensed dose and modelled dose reductions.

To account for selpercatinib dose reductions (in line with dose reductions recommended in the selpercatinib Summary of Product Characteristics [SmPC]),[30] a proportion of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the IAS population of the LIBRETTO-001 trial. The starting doses in the model are provided in Table 29. Following the first cycle, dose reductions for selpercatinib observed in the IAS population of LIBRETTO-001 were applied to calculate the subsequent acquisition cost per four-week period for selpercatinib. The application of dose reductions was performed in this way on the assumption that most patients receiving selpercatinib will experience adverse events (AEs) in the first treatment cycle. The distribution of dose reductions from LIBRETTO-001 applied after the first cycle is presented in Table 30.

ECG costs of monitoring

Due to QT prolongation reported in some patients receiving selpercatinib, the SmPC recommends that the QT interval be monitored more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.[30] Accordingly, the cost of 7 ECGs (one at baseline and once a month thereafter for 6 months) is included in the model in the selpercatinib arm as a one-off cost and removed from the resource use of comparators.

Table 28. 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	
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 29: Weighted drug acquisition costs for selpercatinib in treatment cycle 1 (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, NSCLC	Total cost per treatment cycle, NSCLC
160 mg, twice daily	[redacted]	[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.
Source: Eli Lilly and Company. Data on file.[5]

Table 30: Weighted drug acquisition costs for selpercatinib in treatment cycles 2+ (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, NSCLC	Total cost per treatment cycle, NSCLC
160 mg, twice daily	[redacted]	[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.
Source: Eli Lilly and Company. Data on file.[5]

Appendix J

Revised base-case cost-effectiveness results

A summary of the results in the revised company base case analysis for *RET* fusion-positive NSCLC, using LIBRETTO-001 data from the 16th December 2019 data cut, is presented below.

Base case results

A summary of the base case analysis results (with PAS) is presented in Table 31. The results illustrate that versus all comparators, selpercatinib is associated with greater QALYs, reflecting the high levels of efficacy of selpercatinib in the second line *RET* fusion-positive NSCLC population.

Table 31. Base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,833
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	104,016[a]	69,411
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,833	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

Probabilistic sensitivity analysis (PSA)

The probabilistic base case results are presented in Table 32. The PSA results illustrate that versus both comparators, selpercatinib is associated with greater QALYs. The deterministic and probabilistic base case results are observed to be in close alignment.

Table 32. Probabilistic base-case results second line *RET* fusion-positive NSCLC: selpercatinib PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,809
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,775	69,220
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,809	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET:* rearranged during transfection.

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel are presented in Figure 19.[redacted]

Figure 19. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs. docetaxel monotherapy and nintedanib plus docetaxel

[redacted]

[redacted]

Abbreviations: NSCLC: non-small cell lung cancer; QALY: quality-adjusted life year.

Deterministic sensitivity analysis (DSA)

The tornado diagrams for selpercatinib versus docetaxel and nintedanib plus docetaxel are presented in

[redacted]

Figure 20 and

[redacted]

Figure 21, respectively. The top 25 most influential parameters on the base case are presented in each case.

[redacted]

Figure 20. DSA tornado diagram for selpercatinib versus docetaxel monotherapy

[redacted]

Figure 21. DSA tornado diagram for selpercatinib vs nintedanib plus docetaxel

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Scenario analysis

A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table 33. It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and all comparator arms.

Table 33. Scenario analysis results for selpercatinib versus relevant comparators

Scenario		Pairwise ICER vs. docetaxel	% ICER change	Pairwise ICER vs. nintedanib + docetaxel	% ICER change
	Base case	**£74,833**	**-**	**£69,411**	**-**
1	Utilities, ERG preferred PD value PF: [redacted] PD: 0.569	£77,331	3.34%	£71,495	3.00%
2	Utilities, All pre-progression observations for PF value PF=[redacted] PD=0.628	£76,111	1.71%	£70,660	1.80%
3	Relative dose intensity applied to selpercatinib	£77,454	3.50%	£72,520	4.48%
4	No diagnostic testing costs	£73,377	-1.95%	£67,685	-2.49%
5	TTD equal to PFS curve	£70,517	-5.77%	£64,293	-7.37%
6	Curve choice: OS – Exponential	£59,398	-20.63%	£54,924	-20.87%
7	Curve choice: OS – Weibull	£71,282	-4.75%	£66,044	-4.85%
8	Curve choice: OS – stratified Weibull	£79,456	6.18%	£75,438	8.68%
9	Curve choice: OS – stratified Gamma (selpercatinib and docetaxel arms only)[a]	£70,644	-5.60%	£62,398	-10.10%
10	Curve choice: PFS – Gompertz	£74,236	-0.80%	£68,677	-1.06%
11	Curve choice: PFS – Gamma (selpercatinib and docetaxel arms only)[a]	£79,152	5.77%	£74,625	7.51%
12	Curve choice: PFS – stratified Weibull	£78,961	5.52%	£74,384	7.16%

17	Curve choice: PFS – spline knot 1	£84,462	12.87%	£80,694	16.26%

Footnotes: [a] AFT models were only applied to the selpercatinib and reference arms, whilst base case extrapolations were utilised for nintedanib plus docetaxel so that the hazard ratio from the NMA could be applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity; TA: technology appraisal.

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Clinical expert statement & technical engagement response form

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer [ID3743]

Thank you for agreeing to comment on the ERG report for this appraisal, 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 ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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 return this form by **5pm** on **4 June 2021**

NICE National Institute for Health and Care Excellence

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: ‘academic/commercial in confidence information removed’. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with (RET fusion-positive) advanced NSCLC and current treatment options	
About you	
1. Your name	**James Spicer**
2. Name of organisation	**King's College London; Guy's & St Thomas' NHS Foundation Trust**
3. Job title or position	**Professor of Experimental Cancer Medicine; Consultant in Medical Oncology**
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 advanced NSCLC? ☒ a specialist in the clinical evidence base for advanced NSCLC or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. <u>(If you tick this box, the rest of this form will be deleted after submission.)</u>	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for advanced NSCLC	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Delay disease progression, maintain or improve QoL; extend life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Reduction in tumour size by 30% is conventionally regarded as significant

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in RET fusion-positive advanced NSCLC?	Yes. No approved therapy yet available
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients with RET-rearranged NSCLC receive the same standard care as non-squamous NSCLC without RET-rearrangement, unless there is access to clinical trial. This standard care is 1st line checkpoint inhibitor, platinum doublet chemotherapy (eg pemetrexed/carboplatin), or all 3 drugs in combination, according to tumour PDL1 status and fitness. It is not known whether patients with RET-driven tumours benefit from checkpoint inhibition. Subsequent treatment outside a trial is usually with docetaxel, or docetaxel plus nintedanib, which is toxic and not very effective. My practice is to try to offer these patients a trial instead, as the "standard" care is so poor (despite its mention in various guidelines)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None yet specifically for RET-rearrangement
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Standard of care in the absence of access to RET-directed therapy is as above – there is little controversy about this

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	RET-targeted therapy would be strongly preferred in place of docetaxel, or docetaxel plus nintedanib, in terms of tolerability and response rate. Disease shrinkage in NSCLC is generally associated with symptom improvement
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not yet used outside a trial. This is well-tolerated oral therapy that ca be readily administered as an outpatient in any UK oncology practice
• How does healthcare resource use differ between the technology and current care?	Yes. Docetaxel, or docetaxel plus nintedanib (but not selpercatinib) are commonly associated with major toxicities such as neutropenic sepsis
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Access to RET testing. This is expected to be available as part of the GLH test directory for lung cancer.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Much higher response rate and tolerability is likely to translate into better QoL. OS benefit seems likely, although no direct comparison has been conducted. Another drug in this class is being tested in the first line setting against a platinum/pemetrexed control arm, with cross-over on progression (PFS is primary endpoint)
• Do you expect the technology to increase length of life more than current care?	Yes, as above
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as above
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is only appropriate for the 1-2% of advanced lung cancer with a RET rearrangement
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	Easier and safer than second line docetaxel, or docetaxel plus nintedanib, as above

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.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Tyrosine kinases in solid tumour oncology practice are generally continued until progression, in the absence of intolerable toxicity. Regular disease assessment is with cross-sectional imaging, usually CT scanning. The frequency of these scans would be similar to standard care without a targeted drug, although the duration of treatment (and so total number of scans) may be greater
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?	No
18. Do you consider the technology to be innovative in its potential to make a significant and	Yes, this is the first RET inhibitor to be considered by NICE

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?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	No
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?	Chronic treatment with selpercatinib is well tolerated, especially compared with standard second/subsequent line chemotherapy
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Just a single arm non-randomised trial, so this question is only relevant in that patients in that study were all pre-treated, that is in approximately the same position in the patient pathway as the proposed indication

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response and progression-free survival time are the key endpoints for a single arm trial of a new personalised medicine in cancer
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Response is a good surrogate for PFS. In the pre-treated NSCLC population, a high RR is a useful surrogate for overall survival in some cases. There is a wide body of opinion that prolonged PFS time is meaningful in a disease like NSCLC, where growing tumours quickly contribute to new symptoms and impairment of QoL
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	TA643 refers to entrectinib in ROS1-driven NSCLC, an entirely separate disease. Maybe this is an error.

of NICE technology appraisal guidance TA643?	
23. How do data on real-world experience compare with the trial data?	Anecdotally, trial use of RET inhibitors in RET-driven tumours (my personal experience and that of colleagues) is associated with excellent tolerability and prolonged clinical benefit.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
25. Considering current standard care in the UK, what are the most relevant comparators for selpercatinib in previously-treated	I have discussed this above. Definitive evidence is lacking, but some analyses suggest that patients with RET-driven NSCLC benefit less from checkpoint inhibition that patients without molecular drivers.

RET fusion-positive advanced NSCLC?	
26. What is currently known about RET fusion-positive advanced NSCLC population in terms of patient characteristics and prognostic status?	This genetic lesion is enriched in NSCLC patients who have adenocarcinoma histology and never-smoking status. Its presence is associated with a high risk of brain metastases.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement (please see the executive summary at the beginning of the ERG report for details)	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, 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 appraisal committee meeting. For information: the professional organisation that nominated you has 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 ERG report, these will also be considered by the committee.	
Issue 1: Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	Agreed
Issue 2: LIBRETTO-001 trial survival events and length of follow-up	LIBRETTO-001 was an extended Phase 1 trial, including several tumour types all defined by Ret rearrangement. Definitive data on overall survival is often not available in Phase 1 trials, and there was of course no randomised control arm.
Issue 3: Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice	All had received prior dublet chemotherapy, and more than half had received immunotherapy (some analyses suggest that patients with RET-driven NSCLC benefit less from checkpoint inhibition that patients without molecular drivers). About half of patients had received prior therapy with less potent and less specific RET-directed tyrosine kinase inhibitors. This is expected to reduce the apparent efficacy in the trial population.

Question: Do you agree that prior treatments received in LIBRETTO-001 trial population do not reflect NHS clinical practice? Please explain.	Overall the trial population is not very different from NHS patients who might be treated as part of this TAG indication.
Issue 4: Relevant comparator treatments **Question:** Considering current standard care, do you agree with the ERG that docetaxel (with or without nintedanib) are the most relevant comparators for selpercatinib in the second-line setting? Please explain.	Yes. See also my comments above. These unattractive options are the only "standard" therapies available in this setting.
Issue 5: The relevance of population participating in the trials that provided comparator evidence for the company NMAs **Question:** Do you consider the result of the indirect comparison of selpercatinib	Yes

with docetaxel and docetaxel plus nintadenib to be clinically plausible (see table 20 in the ERG report)?	
Issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	No comment – I don't understand this.
Issue 7: The company modelling of survival for patients receiving selpercatinib **<u>Question:</u>** What proportion of patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with selpercatinib as a second-line treatment? • If they received immunotherapy (pembrolizumab, atezolizumab or	This is very difficult to say. About 20% of non-squamous NSCLC patients receiving pemetrexed, platinum and checkpoint inhibition might be expected to be alive at 5 years, but the great majority of these would not have RET rearrangement or another driver genetic event. As stated above, dominant molecular drivers generally are not associated with major benefit from immunotherapy, presumably because of the low neoantigen burden in these genetically homogeneous tumours. Before the advent of checkpoint inhibitors, the 5 year OS for advanced stage NSCLC was 1-2%.

nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from advanced NSCLC with other molecular drivers?	
Issue 8: The company modelling of survival for patients receiving nintedanib+docetaxel **<u>Question:</u>** What proportion of patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with nintedanib+docetaxel or docetaxel as second-line treatments?	In my opinion this sort of analysis is too speculative to be of value.

• If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from advanced NSCLC with other molecular drivers?	
Issue 9: Progressive disease health state utility value	This question is not self-explanatory
Issue 10: Costing of treatment with selpercatinib	Not my expertise
Issue 11: Cost of testing for *RET* fusions	RET testing is expected to be available as part of the GLH test directory for lung cancer, and therefore will not represent an additional expense above and beyond what is expected to become standard NHS diagnostic practice in the summer of 2020.

Issue 12: NICE End of Life criteria may not be met **Questions:** What is the expected mean survival of people with RET fusion-positive advanced NSCLC receiving second-line chemotherapy (docetaxel with or without nintadenib)? Is it plausible that selpercatinib will increase the survival of people with RET fusion-positive advanced NSCLC by at least 3 months compared with docetaxel with or without nintadenib?	Median PFS with docetaxel with or without nintadenib in this setting is 3 months, and OS 10 months in this context (Reck et al., Lancet Oncology 2014). I would expect selpercatinib to exceed these numbers (PFS in LIBRETTO-001 was 18 months).
Issue 13: Absence of data for subgroups of patients listed in the final scope issued by NICE **Question:** Do you agree with company positioning of selpercatinib in non-squamous disease?	Yes, the prevalence of RET rearrangement is very low in squamous histology.

Are there any important issues that have been missed in ERG report?	No
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • RET rearrangement is rare but detectable in non-squamous NSCLC, the commonest histological subtype. It is overrepresented in never-smokers, and associated with a high prevalence of CNS metastases, a devastating complication in this disease. • There is clear unmet need in this population, as no RET inhibitor is yet routinely available in the UK. • The company suggests use after standard first line therapy, but in place of docetaxel, with or without nintedanib. • The efficacy and tolerability of the alternative docetaxel-based treatment is extremely poor, and many clinicians seek alternative trial option rather than resort to this, even in the absence of an identified molecular driver. • The response rate and PFS with selpercatinib in RET-selected patients are high and very likely to lead to improved QoL and survival compared to otherwise-available 2nd/subsequent line treatment	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

…………………………………………………………………………………………………..

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Selpercatinib for RET fusion-positive advanced non-small cell lung cancer [ID3743]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **4 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise, all information submitted under ‘academic in confidence’ in yellow, and 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 replaced with the following text: ‘academic/commercial in confidence information removed’. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Trial data demonstrating the clinical effectiveness of selpercatinib are only available from the LIBRETTO-001 trial	No	--
Key issue 2: LIBRETTO-001 trial survival events and length of follow-up	No	--
Key issue 3: Prior treatments received by the LIBRETTO-001 trial population do not reflect NHS clinical practice **Question for clinical experts:** Do you agree that prior treatments received in LIBRETTO-001 trial population do not reflect NHS clinical practice? Please explain.	No	--
Key issue 4: Relevant comparator treatments	Yes	Roche agree with the proposed comparators listed by the ERG. Due to the proposed NICE treatment pathway, patients only receive immunotherapy in second-line after first-line treatment with combinations of

Question for clinical experts: Considering current standard care, do you agree with the ERG that docetaxel (with or without nintedanib) are the most relevant comparators for selpercatinib in the second-line setting? Please explain.		platinum doublet chemotherapy and pemetrexed. Clinical expert consultation sought by Roche suggests the number of patients who follow this treatment pathway is small with the majority of patients receiving immunotherapy in first-line. The comparators outlined by the ERG are the most commonly used and therefore should inform the second-line comparators for this appraisal.
Key issue 5: The relevance of population participating in the trials that provided comparator evidence for the company NMAs **Question for clinical experts:** Do you consider the result of the indirect comparison of selpercatinib with docetaxel and docetaxel plus nintadenib to be clinically plausible (see table 20 in the ERG report)?	No	--
Key issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	No	--
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Question for clinical experts:** What proportion of	Yes	Roche would like to query to company's assertation that "*all survival functions have similar fits to the observed Kaplan-Meier data for both the selpercatinib and reference arms*" (Company submission, Section B.3.3.2, page 159) given substantial differences between the best and worst fitting PFS AIC distributions to the observed data with some curves displaying a poor visual fit. Roche do not see

patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with selpercatinib as a second-line treatment? ● If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment ● If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from advanced NSCLC with other molecular drivers?		the approach taken to be a valid approach for curve selection and in line with NICE guidance on decision making (1). Roche note that standard procedure was ignored on the testimony of one clinical expert and wish to query whether this advice was corroborated by other clinical experts who were consulted. Roche note the ERG's comments that "*The ERG considers that the least biased approach to distribution selection is to use the AIC and BIC statistics and choose the top-ranking distributions, unless these distributions are clinically implausible or are a poor visual fit to the totality of the available K-M data*" and "*The ERG highlights that the PFS distributions that ranked above the stratified log-normal distribution overestimate PFS for selpercatinib at the end of the period of time that LIBRETTO-001 trial PFS K-M data are available*" (ERG Report, Section 6.3.3, page 85). Roche wish to clarify: • How the ERG defined clinically implausibility in this setting • That this definition of clinical plausibility consisted of both plausibility of fit to the observed data and long-term plausibility • That clinical plausibility was confirmed by consensus with multiple clinical experts
Key issue 8: The company modelling of survival for patients receiving nintedanib+docetaxel **Question for clinical experts**: What proportion of patients with advanced RET+ NSCLC are likely to be alive at 1-year, 2-	Yes	Roche note the approach taken by the ERG to model docetaxel+nintedanib in Section 6.3.2 (Selpercatinib ERG Report, page 83-84) where the approach was taken to add 0.140 QALYs to the docetaxel monotherapy arm to model docetaxel+nintedanib as per the results of NICE TA347 (2). Roche would like to query whether this simple additive approach is seen as a valid approach for decision making, especially given the differing patient populations and modelling approaches between the current appraisal and NICE TA347. It would be useful for transparency if the ERG were to outline if any other/more

years, 5-years, 10-years if treated with nintedanib+docetaxel or docetaxel as second-line treatments? ● If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment ● If they received chemotherapy as a first-line treatment Is this information based on direct experience with RET fusion-positive NSCLC, or using proxy data, for example from advanced NSCLC with other molecular drivers?		robust approaches were explored/attempted and the reasons why these were seen as not feasible for decision making.
Key issue 9: Progressive disease health state utility value	No	--
Key issue 10: Costing of treatment with selpercatinib	Yes	Roche agree with the ERG that, given the availability of time on treatment data for selpercatinib, this should be used to model treatment costs associated with selpercatinib, as is common practice in NICE appraisals.
Key issue 11: Cost of testing for *RET* fusions	Yes	Roche acknowledge that not all patients are currently routinely tested for RET fusions status in the NHS and that a national NHS Genomic Medicine Service to provide NGS testing is yet to be implemented fully. However, it should be noted

		that, regardless of the outcome of this appraisal, it's the stated aim[1] of the Department of Health and Social care to introduce widespread NGS testing.(3) In the long term, testing will be implemented and therefore the long-term impact of the potential implementation of selpercatinib as standard of care on the cost of testing will be budget neutral. Therefore, Roche feel the omission of testing costs from this appraisal is a valid approach. If a cost of testing is to be included, perhaps an acceptable compromise would be to attribute a small percentage of the overall per person testing costs to selpercatinib, representing the short term additional uptake in testing over and above what the expected testing roll-out would have been. This cost would only be temporary. However, it is acknowledged that this percentage would be difficult to estimate as the rate that the potential introduction of selpercatinib impacts testing is unknown. Scenario analysis could explore this.
Key issue 12: NICE End of Life criteria may not be met **Questions for clinical experts:** What is the expected mean survival of people with RET fusion-positive advanced NSCLC receiving second-line	No	--

[1] *"We will incorporate the latest advances in genomics into routine healthcare to improve the diagnosis, stratification, and treatment of disease"*
"NHS England and NHS Improvement has committed to sequence 500,000 whole genomes by 2023 to 2024, making the NHS the first healthcare service in the world to offer whole genome sequencing routinely and at scale to specific groups of patients."
"With this implementation plan, we set out our priority actions for the financial year 2021 to 2022 which include the following key commitments: [..] proof of concept work, led by Genomics England in partnership with the NHS, to deliver the first phase of a next-generation approach for the diagnosis and treatment of cancer, integrating multiple data sources and new technologies to support faster and more comprehensive genomic testing for cancer in line with the NHS Long Term Plan"
"In 2021 to 2022 we commit to make progress on the following ambitions: [..] progress the NHS Long Term Plan commitment to offer more extensive genomic testing to patients who are newly diagnosed with cancer so that by 2023 over 100,000 people a year can access these tests, including progress on the NHS England and NHS Improvement implementation of pan-cancer panels which are already being rolled out more widely"3. Department of Health and Social Care. Genome UK: 2021 to 2022 implementation plan 2021 [Available from: https://www.gov.uk/government/publications/genome-uk-2021-to-2022-implementation-plan/genome-uk-2021-to-2022-implementation-plan#pillar-1-diagnosis-and-personalised-medicine.

chemotherapy (docetaxel with or without nintadenib)? Is it plausible that selpercatinib will increase the survival of people with RET fusion-positive advanced NSCLC by at least 3 months compared with docetaxel with or without nintadenib?		
Key issue 13: Absence of data for subgroups of patients listed in the final scope issued by NICE **Question for clinical experts:** Do you agree with company positioning of selpercatinib in non-squamous disease?	No	--

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
--	--	No	--

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report 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 ICER
No changes made	--	--	--

1. National Institute for Health and Care Excellence. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA 2013.
2. National Institute for Health and Care Excellence. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer [TA347] 2015 [Available from: https://www.nice.org.uk/guidance/ta347.
3. Department of Health and Social Care. Genome UK: 2021 to 2022 implementation plan 2021 [Available from: https://www.gov.uk/government/publications/genome-uk-2021-to-2022-implementation-plan/genome-uk-2021-to-2022-implementation-plan#pillar-1-diagnosis-and-personalised-medicine.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Selpercatinib for RET fusion-positive advanced non-small cell lung cancer [ID3743]

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- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Eli Lilly and Company Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

NICE National Institute for Health and Care Excellence

Key issues for engagement

issue	Does this response contain new evidence, data or analyses?	Response
issue 1: Trial data onstrating the cal effectiveness of ercatinib are only lable from the RETTO-001 trial	NO	Eli Lilly and Company acknowledge the concerns of the Evidence Review Group (ERG) regarding the single-arm design of the LIBRETTO-001 tr However, as noted by the ERG, there is not an ongoing randomised controlled trial comparing selpercatinib with relevant comparators to the Nati Health Service (NHS) in pre-treated advanced rearranged during transfection (*RET*) fusion-positive patients to resolve this issue. Therefore, furth consideration has been given to the network meta-analyses (NMAs) conducted to compare selpercatinib to relevant comparators in light of the ERG's feedback; please see the Company's response to Issues 5 and 6 for further details.
G comment		Please see the ERG's comments relating to Key Issue 6 for a critique of the company's updated NMA methods.
issue 2: RETTO-001 trial ival events and th of follow-up	YES	Eli Lilly and Company acknowledge the ERG's concerns that the progression-free survival (PFS) and overall survival (OS) data presented in the Company's submission may be associated with uncertainty due to their immaturity.[1] Accordingly, survival data from the 30th March 2020 data cut LIBRETTO-001 are presented in Table 1 below, alongside data from the December 2019 data cut (used in the original Company submission) for ease of comparison. The March 2020 data cut provides data over an additional three-month follow-up period for the 184 patients in the non-smal lung cancer (NSCLC) Integrated Analysis Set (IAS). The 30th March 2020 data cut also provides data from an additional [redacted] eligible efficacy patien (218 eligible efficacy patients in total) with previously treated *RET* fusion-positive NSCLC. Efficacy data for all patients enrolled as of the 30th Mar 2020 data cut-off are presented in full in Appendix B, including Kaplan-Meier plots for PFS and OS (

		[redacted] Figure 5 and Figure 6, respectively).

		The additional data provided by the 30th March 2020 data cut are consistent with the PFS and OS estimates presented in the original submission (16th December 2019 data cut) for second line patients with *RET* fusion-positive NSCLC receiving selpercatinib. As of the 30th March 2020, in the IAS population (including all patients enrolled up to 30th March 2020) there had been 74 progression events (PFS: 74/218 [33.9%]) (

		[redacted] Figure 5, Appendix B) with a median PFS of 19.29 months (95% CI: 16.5–not estimable [NE]) by Independent Review Committee (IRC) assessm (Table 1). This compares to [redacted] progression events ([redacted] and a median PFS of [redacted] ([redacted]) as of the 16th December 20

data cut. The durability of PFS with selpercatinib treatment is supported by the finding that [redacted] ([redacted]) of patients in the IAS who wer enrolled as of 17th June 2019 (N=184) remain progression-free ≥12 months after treatment initiation, as of the 30th March 2020, compared to [redacted] as of the 16th December 2019.

The median OS remains NE, with [redacted] of patients in the IAS (N=184) alive as of the 30th March 2020 data cut. In the IAS population (including all patients enrolled up to 30th March 2020), 41 (41/218 [18.8%]) deaths had occurred up to the 30th March 2020 data cut (Figure 6, Appendix B), compared with [redacted] ([redacted]) deaths up to the 16th December 2019 data cut.

The 30th March 2020 data cut also provides additional data on the objective response rate (ORR) to selpercatinib treatment and the duration of th response (DOR). The ORR as of the 30th March 2020 was [redacted] in the IAS population, which is consistent with the ORR from the 16th December 2019 data cut of [redacted] (Table 1). In NSCLC, there is evidence that improvements in ORR appear to correlate with improvements in OS and PFS.[2, 3] Furthermore, the median DOR in the IAS also remained consistent at 17.5 months (95% CI: 12.1 NE) for all patients enrolled as of the 30th March 2020 data cut, supporting the assertion that treatment with selpercatinib produces a high and durable tumour response that is expected to provide prolonged physical and psychological benefit to patients.

The results presented here from the 30th March 2020 data cut provide further evidence to support the high and durable response rate with selpercatinib, as well as the potential survival benefits of selpercatinib treatment in patients with advanced *RET* fusion-positive NSCLC. The upda results for OS continue to suggest that selpercatinib treatment may confer a survival benefit to this patient group. Data collection from LIBRETTO 001 remains ongoing and subsequent data cuts will become available in due course.

Table 1. PFS and OS for second line *RET* fusion-positive NSCLC patients (IAS) based on IRC assessment

	All patients enrolled as of 17th June 2019		**All eligible efficacy patients enroll as of 30th March 2020**
Data cut	**16th December 2019 N=184**	**30th March 2020 N=184**	**30th March 2020 N=218**
PFS			
Status n (%)			
Event	[redacted]	[redacted]	74 (33.9)
Censored	[redacted]	[redacted]	144 (66.1)
Duration of PFS (months)			
Median	19.32	[redacted]	19.29

95% CI	[redacted]	[redacted]	16.5–NE
Minimum, maximum	[redacted]	[redacted]	0.0+, 30.6+
Rate of PFS (%)			
12 months or more	[redacted]	[redacted]	69.7
95% CI	[redacted]	[redacted]	62.2–75.9
OS			
Status n (%)			
Event	[redacted]	[redacted]	41 (18.8)
Censored	[redacted]	[redacted]	177 (81.2)
Duration of OS (months)			
Median	[redacted]	[redacted]	NE
95% CI	[redacted]	[redacted]	25.7–NE
Minimum, maximum	[redacted]	[redacted]	0.3, 34.5+
Rate of OS (%)			
12 months or more	[redacted]	[redacted]	88.1
95% CI	[redacted]	[redacted]	82.5–91.9
ORR (CR + PR)			
N (%)	[redacted]	[redacted]	124 (56.9)
95% CI	[redacted]	[redacted]	50.0–63.6
Duration of response (months)			
Median	[redacted]	[redacted]	17.51
95% CI	[redacted]	[redacted]	12.1–NE
Minimum, maximum	[redacted]	[redacted]	1.8+, 29.8+
Duration of response follow-up (months)			
Median	[redacted]	[redacted]	11.99
25th, 75th Percentiles	[redacted]	[redacted]	7.4, 15.9

Footnotes: Eligible efficacy 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 selperca
Censored observations are denoted by '+'.

		Abbreviations: CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; NE: not estimable; ORR: obje response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection. **Source**: Eli Lilly and Company Ltd. Data on File (16th December 2019 cut);[4] : Eli Lilly and Company Ltd. Data on File (30th March 2020 cut).[5]
G comment		The ERG agrees with the company that the additional data from the 30th March 2020 data cut are consistent with the ORR, PFS and OS estimate presented in the original CS, but notes that both PFS and OS data remain immature, particularly OS as only 18.8% deaths have occurred and median OS has not been reached in the IAS. The ERG considers that the additional data could have been used within the revised NMAs and economic model to reduce uncertainty in OS and PFS projections for selpercatinib and provide the most up-to-date NMA results and ICERs per QALY gained for selpercatinib versus nintedanib+docetaxel and docetaxel monotherapy.
issue 3: Prior tments received by LIBRETTO-001 trial ulation do not reflect S clinical practice **stion for clinical erts:** Do you agree prior treatments ived in LIBRETTO- trial population do reflect NHS clinical tice? Please ain.	YES	Eli Lilly and Company acknowledge the issue raised by the ERG regarding the prior treatments received by the LIBRETTO-001 trial population.[1] accordance with the eligibility criteria for LIBRETTO-001, and as noted by the ERG,[1] [redacted] patients in the IAS population had received at least one line of platinum-based chemotherapy and [redacted] had received prior immunotherapy. A smaller proportion of patients in the IAS had also received p multi-kinase inhibitor (MKI) therapy ([redacted]). Excluding MKI therapy, which Eli Lilly and Company acknowledge is not currently approved for use by NHS,[6, 7] the prior treatments received by patients in LIBRETTO-001 mirror the therapy regimens currently recommended by NICE in the first line setting in the United Kingdom (UK).[8-11] To address the ERG's concern around prior use of MKIs in the IAS analysis set, Eli Lilly and Company provide survival data for a subgroup of the IAS population, which excludes patients who received prior MKI treatment (N=[redacted]). The patients in this subgroup therefore align more closely with *RET* fusion-positive NSCLC patients in the UK. Data for this subgroup are presented in Table 2 below, with Kaplan-Meier plots for PFS and OS a provided in Figure 7 and Figure 8, respectively, in Appendix C. As of the 30th March 2020 (including patients enrolled up to 30th March 2020), there had been [redacted] progression events in the IAS MKI-naïve subgro ([redacted]% of patients), with a median PFS of [redacted] months (Figure 7, Appendix C). These results compare to [redacted] progression events in the IAS analysi set overall (N=218) ([redacted]% of patients), with a median PFS of [redacted] months as of March 2020. In addition, there were [redacted] deaths in the MKI-naïve subgroup ([redacted]% of patients) as of 30th March 2020, with a median OS of [redacted] (Figure 8, Appendix C). The estimated median OS in the MK naïve subgroup is currently unstable due to the low number of deaths that had occurred as of the 30th March 2020. In the IAS analysis set overall there were [redacted] deaths ([redacted]% of patients) as of 30th March 2020, whilst the median OS was [redacted]. The PFS and OS results for the IAS MKI-naïve subgroup are consistent with the results for the IAS analysis set overall. As the prior therapies received by this subgroup align with the prior therapies that *RET* fusion-positive NSCLC patients in the UK would typically receive, Eli Lilly and

Company consider the results from LIBRETTO-001 to be generalisable to the target patient population in the NHS. Despite the use of MKI treatm in the IAS analysis set, UK clinical experts have also affirmed that the patient population in the LIBRETTO-001 trial is otherwise generalisable to clinical practice in the UK overall.[12]

Table 2. PFS and OS for second line *RET* fusion-positive NSCLC patients (IAS and IAS MKI-naïve subgroup) based on IRC assessment

Characteristic	IAS N=218	IAS MKI-naïve subgroup [redacted]
PFS		
Status n (%)		
Event	74 (33.9)	[redacted]
Censored	144 (66.1)	-
Duration of PFS (months)		
Median	19.29	[redacted]
95% CI	16.5–NE	-
Minimum, maximum	0.0+, 30.6+	-
OS		
Status n (%)		
Event	41 (18.8)	[redacted]
Censored	177 (81.2)	-
Duration of OS (months)		
Median	NE	[redacted]
95% CI	25.7–NE	-
Minimum, maximum	0.3, 34.5+	-

Footnotes: Eligible efficacy 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 selperca Censored observations are denoted by '+'.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: Independent Review Committee; MKI: multi-kinase inhibitor; NE: not estimable; NSCLC: non- cell lung cancer; OS: overall survival; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File (30th March 2020 cut).[5]

		Eli Lilly and Company also acknowledge the ERG's request for data to show whether patients who received platinum-based chemotherapy and immunotherapy received these treatments consecutively or simultaneously.[1] The IAS analysis set of LIBRETTO-001 is comprised of pre-treated patients of mixed treatment lines, including patients at second line, third line and later lines of treatment. For this reason, it is not possible for Eli L and Company to provide data showing whether patients received platinum-based chemotherapy and immunotherapy consecutively or sequential However, the Company has provided a more detailed breakdown of the types of prior treatments received by patients in the IAS analysis set in T 20, Appendix C.
G comment		As stated within the ERG report (Section 1.3), the ERG is aware that this is a LIBRETTO-001 trial post-hoc analysis and not a pre-specified subgroup analysis. Nonetheless, the ERG agrees with the company that the PFS and OS results for the IAS MKI-naïve subgroup are consistent the results for the IAS analysis set overall.
issue 4: Relevant parator treatments **stion for clinical erts:** Considering ent standard care, ou agree with the G that docetaxel n or without edanib) are the t relevant parators for ercatinib in the ond-line setting? se explain.	NO	Eli Lilly and Company have considered the ERG's rationale relating to the relevant comparators for selpercatinib in the second line setting in the NHS.[1] As the ERG highlighted, clinical advice to Eli Lilly and Company indicates that in clinical practice, patients with *RET* fusion-positive NSCLC who receive an immunotherapy at first line would not typically be treated with another immunotherapy in the second line setting. Market research conducted by Eli Lilly and Company indicates that there is a high usage of immunotherapies in the first line setting in the UK (please see Docume B, Section B.1.3.2), meaning only a small proportion of *RET* fusion-positive NSCLC patients would be likely to receive immunotherapies such as atezolizumab, nivolumab and pembrolizumab at second line. Eli Lilly and Company therefore agree with the ERG that immunotherapies should n be considered as relevant comparators to selpercatinib in the second line setting. The ERG have noted that pemetrexed plus carboplatin and platinum doublet chemotherapy may also be considered relevant comparators to selpercatinib in the second line setting.[1] However, market share data provided by Eli Lilly and Company in the original submission (Document B; Section B.1.3.2) highlighted a declining use of platinum doublet chemotherapy ([redacted]) and pemetrexed plus carboplatin ([redacted]) as second line therapies advanced pre-treated non-squamous NSCLC patients in the UK. Two expert clinicians consulted by Eli Lilly and Company also advised that pemetrexed and older chemotherapy regimens are now rarely used in clinical practice. In addition, pemetrexed and platinum-based chemotherap regimens are frequently used with immunotherapies in the first line setting, which further reduces the likelihood that these therapies will be used a second line.[9, 13] Second line market share data obtained by Eli Lilly and Company indicates that docetaxel monotherapy and nintedanib plus docetaxel both have moderate share of the market, at [redacted] and [redacted], respectively. Information provided by clinical experts who were consulted during the revisions to the Company's original submission also supports consideration of nintedanib plus docetaxel and docetaxel monotherapy as relevant comparators to

		selpercatinib in the second line setting. Consequently, Eli Lilly and Company agree that the following treatments are relevant comparators to selpercatinib in second line advanced non-squamous and *RET* fusion-positive UK NSCLC patients: • Docetaxel monotherapy • Nintedanib plus docetaxel The NMA and cost-effectiveness results have been updated for selpercatinib versus these two comparators. Updated cost effectiveness results a summarised in Appendix A and the updated results for the NMA are presented in Appendix F.
G comment		No comment.
issue 5: The vance of population cipating in the trials provided parator evidence he company NMAs **stion for clinical erts:** Do you sider the result of ndirect comparison elpercatinib with etaxel and etaxel plus adenib to be cally plausible (see e 20 in the ERG rt)?	NO	Eli Lilly and Company acknowledge that the trial populations included in the NMA network were likely to have had a low incidence of *RET* fusion-positive patients, given the frequency of *RET* fusions (~1–2%) across all NSCLC cases, which is a limitation of the analysis.[14] However, Eli Lilly and Company were able to adjust the docetaxel plus placebo arm (or pseudo-control arm), for the effect of *RET* on patient surv using real world evidence data from *RET* fusion-positive and negative patients in the Flatiron CGDB database (please see Section D.1.7 in the Appendices of the Company's original submission for further details). As part of the Company's revised indirect treatment comparison (ITC) approach, described in detail in response to Issue 6, further differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 the pseudo-control arm were adjusted for using propensity score matching. It was not possible to control for *RET* in the rest of the network, as the *RET* status of patients in the other studies included in the network was not reported. Nevertheless, as part of the revised ITC Eli Lilly and Company used meta-regression on the network, to relate the size of treatment effe obtained from the meta-analysis to numerical characteristics of the included trials, with the aim of explaining as much of the observed between-tr heterogeneity and mitigating this uncertainty as much as possible. As detailed in Table 21, Appendix D the difference in deviance information criterion (DIC) values between key covariates was <4 in most cases, indicating minimal heterogeneity in the network. This suggested that numeri differences in characteristics between trial populations included the network were unlikely to be having a significant impact on survival outcomes. The difference in DIC between the fixed effects (FE) model with no covariates ([redacted]) and the FE model adjusted for age ([redacted]) was >4. However, inclusion of an age adjustment, which was used in the original Company submission, resulted in model overfitting for nintedanib plus docetaxel, which produced unrealistic estimates of OS. Further details can be found under the 'NMA meta-regression and model selection' section, in respo

		to Issue 6. Exclusion of age from the NMA resulted in more clinically plausible OS estimates for nintedanib plus docetaxel versus docetaxel (plea see revised NMA results presented in Table 25, Appendix F. While Eli Lilly and Company therefore acknowledge that it was not possible to mitigate all uncertainty related to the low incidence of *RET* in the tr populations included in the network, the Company adopted an approach that endeavored to simulate a clinically relevant population and plausible comparative survival estimates for relevant comparators to selpercatinib, within the confines of the limited data available.
G comment		The ERG acknowledges the attempts of the company to mitigate uncertainty in the NMAs within the confines of the limited and heterogeneous da available. Please see the ERG comments relating to Key Issue 6 for a critique of the updated NMA methods, including the network meta-regressions undertaken by the company.
issue 6: ertainty associated the pseudo-control erence) arm used to nect selpercatinib etwork meta- ysis	YES	Eli Lilly and Company acknowledge the concerns raised by the ERG surrounding the targeted minimum loss-based estimation (TMLE) method.[1] improve the robustness of the ITC, the methodology has been updated using propensity score matching to estimate treatment effects between selpercatinib and relevant comparators. This approach provided a more clinically plausible PFS estimate for the pseudo-control arm, whilst samp size was not significantly decreased after the matching process. A description of the updated method using propensity score matching is provide below. Relevant code for propensity score matching and the NMA are available in Appendix E. **Propensity score matching approach** As described in the original Company submission (Document B, Section B.2.8), the first step in the generation of the pseudo-control arm was the adjustment for *RET* fusion status using data from the Flatiron Clinico-Genomic database (CGDB). This step remained the same for the revised IT approach. Full details of the methods used in the analysis of the Flatiron CGDB were presented in the Company's original submission (Appendic Section D.1.7). Following adjustment of the pseudo-control arm for *RET* fusion status, further differences in prognostic factors between the selpercatinib arm fro LIBRETTO-001 and the docetaxel plus placebo arm from REVEL were adjusted for using propensity score matching with a multivariable regressi approach.[15] The covariates that were used as adjustment factors during propensity score matching are summarised in Table 3. Adjustment for further prognostic factors beyond *RET* status between the selpercatinib and docetaxel plus placebo arms was necessary to account for any furth differences between trial populations, and to generate a reliable treatment effect estimate between the two treatments, such that selpercatinib co be joined to the full network.

		A summary of the baseline patient characteristics of the LIBRETTO-001 and REVEL trial populations, alongside data showing the impa of adjustment for *RET* and other prognostic factors is provided in Table 23. Summary of patient characteristics of the REVEL and LIBRETTO pre-treated NSCLC trial populations, before and after adjustment for *RET* fusion status and the propensity score matching process

Characteristic	Baseline characteristics		After *RET* adjustment Before propensity score matching		After propensit score matching
	LIBRETTO-001, IAS (selpercatinib) (N=184)	REVEL (docetaxel + placebo) (N=447)[b]	Selpercatinib arm (N=174)[c]	Docetaxel + placebo arm (N=447)	Docetaxel + placebo arms (N=174)
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology: Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≥ 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis to start of trial (median months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] The analysis followed greedy match as the matching algorithm. [b] A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to gen the pseudo-control arm. [c] The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the ne exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on cova required for the matching process.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS, Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-sma lung cancer; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on File.(7)

, Appendix F.

Table 3. Summary of patient characteristics of the REVEL and LIBRETTO trial populations for second-line NSCLC

Characteristic	REVEL (docetaxel + placebo) (N=625)	LIBRETTO PAS (N=105)	LIBRETTO IAS (N=184)
Age (years)			
Median	[redacted]	61	62
Gender (%)			
Female	[redacted]	59.0	57.1
Race (%)			
White	[redacted]	52.4	46.7
Asian	[redacted]	38.1	44.6
Other	[redacted]	[redacted]	[redacted]
Smoking history (%)			
Never smoked	[redacted]	71.4	67.9
Histology (%)			
Non-squamous	[redacted]	[redacted]	[redacted]
ECOG performance score (%)			
ECOG ≥ 1	[redacted]	70.5	64.2
History of prior surgery (%)			
Prior surgery	[redacted]	[redacted]	45.7
Stage at diagnosis (%)			
Stage IV	[redacted]	96.2	92.5
Time since diagnosis to start of trial (months)			
Median	[redacted]	30.1	24.2
Sum of longest diameters of tumors (mm)			
Median	[redacted]	60.0	54.7
Metastatic sites (%)			
≥ 2 metastatic sites	[redacted]	[redacted]	[redacted]

CNS metastases at baseline	[redacted]	35.2	32.6

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group, IAS, integrated analysis set (all patients treated with platinum-b chemotherapy); NR, not reported; NSCLC: non-small cell lung cancer; PAS, Primary Analysis Set.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Propensity score matching uses individual patient data (IPD) from one data set to produce weights 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.[15] Specifically, matching aims to replicate randomisation by identifying control individuals who are similar to the treat individuals in one or more characteristics.[16] By matching the outcomes of individuals who differ in the treatment variable, but are otherwise observationally similar, this approach enables estimation of the treatment effect.[16]

A multivariable regression model was used to estimate propensity scores and match data from the docetaxel plus placebo and selpercatinib arms Guidance provided in NICE TSD17 informed the propensity score matching process.[16]

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 treatment effect and estimate log (hazard ratios) and standard errors for selpercatinib versus pseudo-control arm (Table 4). The hazard ratio was then introduced into the NMA of second line treatments described previously in the Company submission.

Table 4. Estimated treatment effects for selpercatinib versus docetaxel (pseudo-control arm) in second line patients

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

Abbreviations: CrI: credible interval; OS: overall survival; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

The Kaplan-Meier outputs for PFS and OS, from the time acceleration adjustment for *RET* and the adjustment for further prognostic factors throu matching using propensity scores, are presented below in Figure 1a and b.

Figure 1. Kaplan-Meier charts for selpercatinib and docetaxel pseudo-control arm in second line advanced NSCLC patients following th time acceleration adjustment for *RET* and propensity score matching

(A) PFS[a]

		[redacted]

(B) OS[a]

[redacted]

Footnotes: [a] The selpercatinib arm was not adjusted for *RET*, as all patients in LIBRETTO-001 were *RET* fusion-positive. In the selpercatinib arm, propensity score matching had little effect on survival outcomes and consequently the 'original and *RET*-adjusted' and 'PSM-adjusted' selpercatinib curves are superimposed for both PFS and OS.
Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; PSM: propensity score matching; *RET:* rearranged during transfe
Source: Eli Lilly and Company Ltd. Data on File.[5]

The impact of the adjustment for *RET* fusion and other prognostic factors can be seen to have made the OS estimate for docetaxel more optimis whilst the adjustment had little effect on OS in the selpercatinib arm. Clinical opinion suggested that following the revised adjustment process, an artificial overestimation of OS remained in the pseudo-control arm ([redacted]). This is supported by a recent observational study that utilise Flatiron CGDB data to compare OS based on *RET* status, before and after adjustment for covariates, which found that despite *RET* fusion-positiv patients having favourable OS compared with patients without a *RET* fusion, there were no significant differences in OS based on *RET* status aft adjustment for baseline covariates.[18] In addition, median OS for advanced NSCLC patients, without a *RET* fusion, receiving docetaxel has been reported at 9.1 months.[17] Further published data supporting limited survival for non-targeted treatments in pre-treated *RET* fusion-positive NSCL are presented in response to Issue 12. Altogether, these data support our assertion that OS was overestimated in the pseudo-control arm as a re of the Flatiron *RET* adjustment and propensity score matching (Figure 1).

However, the adjustment process had a smaller impact on the PFS estimate for the docetaxel arm, which was considered by clinical experts to b clinically plausible PFS estimate for the pre-treated advanced non-squamous *RET* fusion-positive NSCLC population. As such, Eli Lilly and Comp believe that the updated NMA method, using propensity score matching, provides more robust PFS survival estimates for selpercatinib versus th pseudo-control (reference) arm. Although OS estimates for the docetaxel plus placebo pseudo-control arm remain an overestimation, the impact this on subsequent cost-effectiveness analyses is that the cost-effectiveness results for selpercatinib are likely to be conservative, as the true difference in treatment effect on OS between selpercatinib and comparators has not been fully realised.

NMA meta-regression and model selection

A meta-regression was explored to relate the size of the treatment effects obtained from the meta-analysis to certain numerical characteristics of included trials, with the aim of explaining as much of the observed between-trial heterogeneity as possible. In line with the approach taken in the Vickers et al. study,[19] meta-regression was used to explore the following study level covariates: median age, ECOG status ≤1, proportion male, proportion programmed death ligand-1 (PD-L1) positive and proportion Asian. Covariates were included one at a time to see if they improved mo fit. Both random effects (RE) and fixed effects (FE) hierarchical exchangeable models were explored for all outcomes. The models, with or withou the inclusion of covariates, were assessed for model fit for OS, PFS and ORR, using DIC. Model fit statistics for the models explored are included Table 21, Appendix D. Lower DIC values represent better model fit.

The feasibility of conducting a hierarchical exchangeable model, to account for PD-L1 status, was also explored, given the global nature of the N and the inclusion of treatments dependent on a patient's PD-L1 status. However, it was not possible to include REs for the hierarchical exchangeable model because of a limited number of parameters; therefore, an FE approach was selected.

For OS and PFS, the FE hierarchical exchangeable model that was adjusted for age corresponded to the lowest DIC value, suggesting it had a better fit (see Appendix D, Table 21). This model was used in the original NICE submission. However, visual assessment of the relationship betw OS versus age for nintedanib plus docetaxel suggested that there was evidence of overfitting, with increasing age predicting unrealistic estimates OS. It is difficult for an NMA to accurately predict the effect of a covariate when restricted to summary level data, and therefore the effect of age r have been overestimated by the meta-regression. As such, a cautious approach was taken whereby a FE hierarchical exchangeable model, with

		age adjustment, was selected for OS and PFS in the revised NMA. For ORR, an FE hierarchical exchangeable model was selected, adjusted for proportion of Asian patients. **NMA results** Updated results from the NMA, generated using the adjustment for *RET* positive status, the propensity score matching approach described abov FE hierarchical exchangeable model for OS and PFS, and a FE hierarchical exchangeable model adjusted for the proportion of Asian patients fo ORR, are available in Appendix F. The results of the revised NMA have also been incorporated into the cost-effectiveness results presented at Technical Engagement.
G comment		**<u>ERG summary of revised company NMAs</u>** As part of their technical engagement response, the company has revised the second stage of generating OS and PFS pseudo-control arms usi propensity score matching approach. The company has also provided updated NMA results and performed network-meta regressions. Updated results are based on revised OS and PFS treatment effect estimates for selpercatinib compared to the (docetaxel) OS and PFS pseudo-control arms. The company presented revised OS and PFS results from an FE hierarchical exchangeable NMA model (without age adjustment as used i the original CS). The company also presented ORR from an FE hierarchical exchangeable NMA model, with adjustment for the proportion of Asi patients (as used in the original CS). **<u>ERG critique of propensity score matching approach</u>** The ERG considers that the company rationale for using the propensity score matching approach (an approach that aims to adjust the OS and P selpercatinib arms and pseudo-control arms for differences in the populations by matching baseline characteristics) is clear. The adjustment factors used in the propensity score matching approach are also clear (Appendix F, Table 23). The ERG notes that the adjustme factors used in the propensity score matching approach are a subset of the factors identified as being associated with *RET*+ fusion status and us in the first stage of generating the pseudo-control arms (CS, Appendix D.1.7). The general approach to propensity score matching is also clear, i.e., multivariable regression using a greedy matching algorithm (a method usin sampling without replacement [i.e., each person is matched only once]) to calculate weights using IPD from the LIBRETTO-001 trial and the REV trial to match the baseline characteristics of patients from the OS and PFS pseudo-control arms to the selpercatinib arms.

		The ERG notes that the OS and PFS treatment effect estimates for selpercatinib versus the pseudo-control arm following the revised approach (Table 4) are smaller (i.e., a greater advantage to selpercatinib over the pseudo-control arm for both OS and PFS) than the original treatment effe estimates (CS, Table 34). The ERG highlights three issues relating to uncertainty around the propensity matching approach. • First, as reported in TSD17 (Section 2.3.5), propensity score matching methods rely on an assumption of overlap of covariate distribution, bo before and after matching. In other words: "…*for any combination of covariates, there is always the chance of seeing individuals in both the treatment and the control groups. It rules out the possibility that some individuals with certain observable characteristics are always in one group and never in the other*." (TSD 17, p18) • The company has not presented any evidence to demonstrate that formal checks of overlap of covariate distribution, before or after matching were carried out. The ERG considers that, before matching, clear differences are present between the patients in the LIBRETTO-001 trial an the REVEL trial for most of the characteristics used in the matching process (particularly sex, proportions of White and Asian participants, proportions never smoked and time since diagnosis, Table 23, Appendix F). Overlap can be improved by matching, but the ERG notes that differences still seem to be present for sex, proportions of White and Asian participants and time since diagnosis after matching. The impact o any remaining differences in covariate distribution after matching on the OS and PFS treatment effect estimates for selpercatinib compared to the pseudo-control arm is unknown. • Second, the company states that a multivariable regression model has been used for propensity score matching and has presented statistica code (Appendix E) for propensity score matching approaches using a logistic regression model and also using a generalised boosted model, flexible method for estimating propensity scores which can adjust for a large number of covariates and incorporate functions of covariates including polynomial terms and interactions between covariates. However, it is not clear which of these approaches was applied to the patien characteristics presented in Appendix F (Table 23) and, consequently, then used to generate the OS and PFS treatment effect estimates for selpercatinib versus docetaxel (pseudo-control arm) presented in Table 4 and the K-M plots presented in Figure 1. Furthermore, the compan has not explained their rationale for the choice of regression model (logistic and/or generalised boosted model), nor presented any assessme of the statistical model specification or model fit.

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		• Third, compared with the original approach, data from fewer patients were included in the propensity score matching approach. Ten patients from the LIBRETTO-001 trial IAS (n=184) were excluded as data on covariates required for the matching process were missing. The number patients with non-squamous NSCLC from the REVEL trial who provided data was reduced from 447 patients to 174. **ERG critique of revised NMA methods and results** The ERG considers that the NMA methods used by the company (including network meta-regressions to examine between-trial heterogeneity), a the company approach to model selection were appropriate. In particular, the ERG's preference is that clinical plausibility of estimates be conside for all models and that model fit (e.g., DIC statistics) is assessed only for models that generate clinically plausible estimates. Results from the revised company NMAs demonstrated statistically significant advantages for selpercatinib versus docetaxel plus placebo and nintedanib+docetaxel versus docetaxel plus placebo for both OS and PFS (Table 26, Table 27). The selpercatinib versus docetaxel plus placebo nintedanib+docetaxel versus docetaxel plus placebo HRs are smaller (i.e., larger advantages for selpercatinib and nintedanib+docetaxel when th treatments are compared with docetaxel plus placebo) compared to the original NMA results (CS, Table 36 and Table 37). It does not appear that the company has made any revisions to the ORR NMAs presented in the CS. The NMA model used in the original CS (FE hierarchical exchangeable NMA model, with adjustment for the proportion of Asian patients) appears to be the same as that used in this technica engagement response. Therefore, it is unclear why results from the ORR NMAs resented in Appendix F are different to the original results preser in the CS (Table 35) and the company response to clarification question A13. **ERG conclusions of revised company NMAs** The ERG acknowledges the detailed analyses conducted by the company to attempt to generate a robust pseudo-control arm to "simulate a clini relevant population and plausible comparative survival estimates" within their NMAs and the awareness of the company in their technical engagement response that it is not possible to mitigate all uncertainty in their estimation of indirect treatment effect estimates for selpercatinib compared to relevant comparators. The uncertainties and concerns relating to the use of the TMLE method highlighted in the ERG report have become obsolete by the company's u of a propensity score matching approach. However, there are some areas of uncertainty around the use of the propensity matching approach,

		particularly relating to the 'overlap' of the covariate distribution in the selpercatinib and pseudo-control arms following matching. Further, the revis pseudo-control arm OS estimates still appear to be over-estimates. It should be noted that many other concerns regarding data input and methods used within the NMAs, as highlighted within the ERG report (Sect 3.6.3 and Appendix 9.2), remain, namely: • the trials included in the networks (other than the LIBRETTO-001 trial) do not reflect a *RET*+ NSCLC population, nor have these networks b adjusted for any prognostic factors associated with *RET*+ NSCLC • the inclusion of data from comparators in the NMAs which are not relevant to the decision problem introduces uncertainty into the NMA result • the ORR NMA used raw (unadjusted) data from the docetaxel+placebo control arm of the REVEL trial and selpercatinib data from the LIBRET 001 trial; this approach introduces uncertainty into the ORR NMA results • differences in the definition of PFS between the REVEL trial, the LIBRETTO-001 trial, and the Flatiron database (used in the first stage of genera the pseudo-control arms) are likely to have introduced uncertainty into the generation of the PFS pseudo-control arm, and therefore into the NMA results • there was evidence of violation of the assumption of proportion hazards (PH) for three trials in the PFS NMA and for two trials in the OS NMA Section 3.6.3 of the ERG report for details of the trials). Additional analyses using a fractional polynomial approach were conducted by the comp for the PFS NMA. Using a fractional polynomial approach was deemed inappropriate by the company for OS due to the immaturity of LIBRETTO-001 trial OS data. The impact of PH violation on the results of the OS NMA is not known. The ERG also notes that the additional data presented in response to Key Issue 2, which reflect a larger sample size and longer duration of follov up, were not used within the company revised NMAs. Given the inherent uncertainty that remains, despite the best efforts of the company, the ERG considers that definitive conclusions regarding the direction and magnitude of the relative effect of selpercatinib versus the comparators still cannot be made from the revised company OS and PFS NMAs.
issue 7: The pany modelling of ival for patients iving selpercatinib	YES	Please see the response to Issue 8 below for additional evidence on the revised survival curves for selpercatinib, docetaxel, and nintedanib plus docetaxel.

stion for clinical erts: What ortion of patients advanced RET+ LC are likely to be at 1-year, 2-years, ars, 10-years if ed with ercatinib as a nd-line treatment? • If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment is information ed on direct erience with RET n-positive NSCLC, sing proxy data, for mple from advanced LC with other ecular drivers?		

G comment		Please see ERG comments relating to Key Issue 8.
issue 8: The pany modelling of ival for patients iving edanib+docetaxel **stion for clinical erts**: What portion of patients advanced RET+ CLC are likely to be e at 1-year, 2-years, ars, 10-years if ted with edanib+docetaxel or etaxel as second- treatments? • If they received immunotherapy (pembrolizumab, atezolizumab or nivolumab) as a first-line treatment • If they received chemotherapy as a first-line treatment	YES	Eli Lilly and Company acknowledge that the ERG’s preferred survival function for the docetaxel plus placebo pseudo-control (or reference) arm, based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) rankings, was the stratified lognormal function.[1] Implementing the ERG’s preferred modelling of OS in the Company’s original model for patients receiving docetaxel, and subsequently adding a quality-adjusted life year (QALY) gain to represent additional health-related quality of life (HRQoL) and survival benefits associated with nintedan plus docetaxel, generated a mean OS of [redacted] months for nintedanib plus docetaxel. The 5-year survival for patients receiving nintedanib plus docetaxel or docetaxel monotherapy using the original Company methodology ([redacted]; see [redacted] Figure 2) is high compared to published survival rates for other NSCLC populations, which the ERG acknowledges. Implementing the ERG’s preferred modelling of OS in the Company’s revised model for patients receiving docetaxel generates similarly consistently high predicted survival rates for docetaxel ([redacted] at 5 years; see Tabl

is information ed on direct erience with RET on-positive NSCLC, sing proxy data, for mple from advanced CLC with other ecular drivers?		5). The ERG supports their approach by noting that whether the 5-year survival is optimistic or pessimistic for patients with *RET* fusion-positive NSCLC, treated in the second- or later-line setting after receiving prior immunotherapy, is unknown.[1] [redacted] **Figure 2. OS for selpercatinib, docetaxel monotherapy and nintedanib plus docetaxel (Company base case and ERG alternative)** **Footnotes:** OS extrapolation obtained from the ERG report for selpercatinib in NSCLC, page 86. **Abbreviations:** ERG: Evidence Review Group; KM: Kaplan-Meier; OS: overall survival. Following recommendations from the ERG,[1] Eli Lilly and Company sought further clinical expert opinion regarding survival estimates for pre-treat advanced *RET* fusion-positive NSCLC patients. Two expert clinicians practising in the UK were asked to provide survival estimates for patients receiving selpercatinib or docetaxel monotherapy, who had been previously treated with an immunotherapy. The survival estimates are provided

Table 5 alongside the projections for docetaxel monotherapy using the Company's original and revised model, which were generated using the stratified lognormal function, as preferred by the ERG.

Clinical expert opinion does not support the ERG survival projections using the stratified lognormal curve for docetaxel. The experts consulted indicated that patients receiving docetaxel monotherapy as second line treatment would be unlikely to survive for more than 24 months on averag and that the NICE End of Life Criterion (for short life expectancy) was expected to be met for this patient population. This is reflected in the surviv estimates provided by the two clinicians in Table 5, where [redacted] of *RET* fusion-positive patients receiving docetaxel monotherapy afte immunotherapy are anticipated to be alive after 5 years. Survival projections from the expert clinicians after 5, 10, 20 and 25 years for pre-treatec *RET* fusion-positive patients receiving docetaxel monotherapy were consistently substantially lower than the predictions informed by the stratifiec lognormal docetaxel curve applied using the Company's original evidence synthesis methods and survival analyses, and in the Company's revise analyses and model.[1] In addition, the ERG's prediction that [redacted] (Company's original model), or [redacted] (Company's revised model) of patients receiv docetaxel monotherapy would be alive after 25 years is not plausible, as it is unlikely any patients with metastatic disease would reach age 84 (as per the starting age of 59.4 years in the base case analysis). Expert clinician feedback therefore suggests that the ERG's survival estimates for patients treated with docetaxel monotherapy in the second line are an overestimation and unrealistic for this patient population.

Since the QALY increment for nintedanib plus docetaxel is added to this overestimated docetaxel arm, the ERG's estimate of [redacted] months mean for the nintedanib plus docetaxel arm using the Company's original model is also anticipated to be a significant overestimation. It is further noted the QALY gain added for nintedanib plus docetaxel was sourced from a cost-effectiveness analysis for a broad population of advanced NSCLC patients, and therefore does not consider any prognostic factors influencing survival associated with the presence of a *RET* gene fusion.

With regards to the clinician estimates for selpercatinib, a published median OS estimate of 49.3 months has been reported in *RET* fusion-positiv patients receiving selective *RET* tyrosine kinase inhibitors, which could suggest that the clinicians 5-year survival estimates may be pessimistic, although estimates were from a small population (n=60) and using a retrospective study design.[20]

Table 5. Survival projections for previously treated patients receiving docetaxel monotherapy or selpercatinib

Population	5-year survival (%)	10-year survival (%)	20-year survival (%)	25 year-survival (%)
ERG model predictions using Company's original model[a]				
RET fusion-positive patient receiving docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
ERG model predictions using Company's revised model[b]				

RET fusion-positive patient receiving docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Clinical expert one				
Patient receiving docetaxel monotherapy after prior immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving docetaxel monotherapy after immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving selpercatinib[c]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical expert two				
Patient receiving docetaxel monotherapy after prior immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving docetaxel monotherapy after immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion-positive patient receiving selpercatinib[c]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Docetaxel survival projections using the stratified lognormal extrapolation for docetaxel monotherapy used in the originally submitted Company cost-effective model. [b] Docetaxel survival projections using the stratified lognormal extrapolation for docetaxel monotherapy used in the revised Company cost-effectiveness mod technical engagement. [c]both clinical experts were hesitant to give reliable prediction beyond 5 years due to lack of long-term data for *RET*-targeted therapies in NS therefore, predictions for selpercatinib beyond 5 or 10 years are uncertain and listed as unknown.
Abbreviations: ERG: Evidence Review Group; *RET*: rearranged during transfection.

Revised survival extrapolations

Given the revisions to the NMA approach to produce more reliable survival estimates in the *RET* fusion-positive NSCLC population (see the response to Issue 6), it was necessary to generate an updated set of survival extrapolations for selpercatinib and docetaxel monotherapy. PFS a OS functions for the other relevant comparator (nintedanib plus docetaxel) were constructed through the application of the hazard ratio generated the revised NMA to the reference (docetaxel) arm extrapolation (Table 6). For the selpercatinib arm, as IPD were available to inform long-term extrapolations for PFS, it was not necessary to apply a hazard ratio to the reference arm to generate these.

Table 6. Hazard ratios (95% CrI) applied to reference arm (FE hierarchical exchangeable)

Drug (patient subgroup)	PFS	OS
Docetaxel monotherapy	NA	NA
Nintedanib + docetaxel	[redacted]	[redacted]

Abbreviations: CrI: credible interval; FE: fixed effects; NA: not applicable: OS: overall survival; PFS: progression-free survival

Progression-free survival

Model fit statistics for the parametric survival functions are available below in Table 7 and long-term extrapolations for PFS are available in Apper G, Figure 15 and Figure 16. Among all the curves explored, minimal difference between the AIC and BIC statistics was observed, although the be fitting curve, as indicated by both the AIC and BIC statistics, was the unstratified Gamma.

Table 7. Model fit statistics for PFS second line parametric survival functions for selpercatinib and reference arm

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Unstratified				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified				
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

		Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival. All the selected curves presented to the clinical experts produced consistent predicted medians for selpercatinib (range [redacted] months), except for stratified lognormal. The experts indicated that for *RET* fusion-positive patients treated with either selpercatinib or docetaxel, many of the curves were predicting over-optimistic estimations of long-term PFS. Curves that produce longer tails, as seen with immunotherapies, would not be seen with targeted therapies such as selpercatinib. In this respect, the Gompertz (stratified or unstratified) were deemed the most realistic curves; the stratified curve was ultimately selected to account for proportional hazards violation observed in the PFS NMA and the need to apply a hazard ra to generate the PFS estimate for nintedanib plus docetaxel. The stratified Gompertz produced consistent predictions to the observed trial data fro LIBRETTO-001 (predicted = [redacted] months vs observed = [redacted] months) but generated a smaller tail and only a small % remaining progression-free after 5 years. The revised Company base case extrapolations for selpercatinib and comparators for PFS is presented in Figure 3. As the best fitting curve according to goodness-of-fit statistics, the unstratified Gamma function is applied in a scenario analysis.

Figure 3. Revised Company base case extrapolations for selpercatinib and comparators for PFS, stratified Gompertz

[redacted]

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

Overall survival

Model fit statistics for the parametric survival functions are provided in Table 8, and long-term extrapolations for OS are available in Appendix G, Figure 17 and Figure 18. Among all the curves explored, minimal difference between the AIC and BIC statistics was observed, although the best fitting curve, as indicated by both the AIC and BIC statistics, was the exponential and Weibull as the second best fitting curve

Table 8. Model fit statistics for OS second line parametric survival functions for selpercatinib and reference arm

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Unstratified				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Spline/knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified				
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Feedback from the clinical experts suggested that the adjustment made to the docetaxel reference arm, through application of the time accelerati factor and propensity score matching using multivariable regression, had resulted in overly optimistic estimations for OS. Both experts estimated approximately [redacted] of *RET* fusion-positive patients receiving docetaxel would be alive after 5 years, [redacted] after 10 years and [redacted] after 25 years (Ta 5). As a result, an overly optimistic prediction for OS in nintedanib plus docetaxel was also anticipated, following the application of the hazard rati from the NMA.

Clinical expert feedback suggested that the most plausible extrapolations for OS for both arms was achieved using the stratified Gamma, stratifie Weibull or Spline/Knot=1 survival function. An illustration of the predicted survival rates produced from a selection of curves presented to the exp are shown in Table 9 below.

Table 9. Long-term predicted survival estimates with the Stratified Weibull, Spline/Knot=1 and Stratified Gamma

	Median PFS[a] (months)	Median OS (months)	5-year	10-year	25-year
Exponential					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified loglogistic					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline/Knot 1					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Stratified Gamma					
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]fixed by applying the stratified Gompertz.
Abbreviations: OS: overall survival; PFS: progression-free survival.

The predicted survival rates at 5-,10- and 25-years were similar for both selpercatinib and docetaxel for stratified Weibull, Spline/Knot=1 and stratified Gamma, and produced consistent long-term predictions at 10- and 25-years compared to those provided by the clinical experts in Table For the Spline/Knot=1, 10-year survival was predicted by the model at [redacted] and [redacted] for selpercatinib and docetaxel, respectively, compared to [redacted] and [redacted] estimated by the clinical experts for selpercatinib and docetaxel, respectively. In contrast, more conservative curves such as the Gompe predicted a 5-year survival for selpercatinib ([redacted]) that was more consistent with estimates provided by clinical experts ([redacted]), compared to the stratified Weibull ([redacted]), Spline/Knot=1 ([redacted]) and stratified Gamma ([redacted]), but much lower 10-year survival rates at [redacted] and [redacted] for selpercatini and docetaxel, respectively, compared to those estimated by the clinical experts. As such, the stratified Weibull, Spline/Knot=1 and stratified Gar were considered to, overall, provide a more clinically plausible OS estimate than the more conservative Gompertz.

The stratified Weibull was the most conservative option and stratified Gamma most optimistic out of the three curves preferred by the experts. Consequently, the Spline/Knot=1 function was applied due to the application of hazard ratios and assumption of proportional hazards for ninteda and docetaxel to docetaxel, and as it produced an extrapolation in-between the stratified Weibull and stratified Gamma distributions. Although sp based models may not have a theoretical distribution, they can be used to fit survival curves where several 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 associat with the disease, and therefore different exponential, Weibull, or log-normal distributions may exist within the data. Accordingly, the use of spline-based models is a relatively simple method of modelling complex survival data, and when only the intercept of a spline-based model varies by treatment, this provides a proportional hazards model (thus making it acceptable for a treatment effect hazard ratio to be applied).

The recommended base case extrapolations for selpercatinib and comparators for OS is presented in Figure 4.

		Figure 4. Base case extrapolations for selpercatinib and comparators for OS, Spline/Knot=1 [redacted] **Abbreviations**: KM: Kaplan-Meier; OS: overall survival. **Scenario analyses** Scenario analyses for PFS included using the unstratified Gamma, Gompertz, stratified Weibull and Spline/Knot=1. Scenario analyses for OS included the unstratified exponential and Weibull as the two best fitting distibutions, and stratified Weibull and stratified Gamma as alternative clir expert choices. Results from the scenario analyses are presented in Appendix J.
S comment		The company's rationale for calculating combined AIC and BIC statistics rather than independently calculating AIC and BIC statistics for each treatment arm and then selecting the best fitting distribution for each treatment arm (based on independent AIC and BIC statistics, visual inspecti and clinical opinion) remains unclear. Nevertheless, the ERG is satisfied that the company's choices of PFS distribution for each treatment arm a reasonable. However, the ERG considered that the company's approach, presented in the CS, to selection of OS curves was too subjective and

		ERG still considers that the company approach to selection of OS curves is too subjective. The OS distribution the company has now chosen estimates 5-year survival for patients treated with selpercatinib and docetaxel at 37.2% and 9.0% respectively. In contrast, company clinical expe estimates of 5-year survival are between xx% and [redacted]% for patients treated with selpercatinib, and between [redacted]% and [redacted]% for patients treated with docetaxel. Whilst the company model 5-year survival estimate for patients treated with docetaxel lies within the lower and upper bound estimates provided by clinical experts, the model estimate for patients treated with selpercatinib (37.2%) is considerably higher than company expert opinio ([redacted]% to [redacted]%). Further, all the distributions considered by the company as possible options for modelling OS for patients treated with selpercatinib have at least 9% more people alive at 5 years than the upper bound company clinical experts' estimate and thus all distributions appear clinically implausible. In addition, visual inspection of Figure 4 suggests that whilst the selpercatinib OS K-M data appear to be heavily censored after 20 months, the available data after 20 months suggest that the distribution chosen by the company to model OS for patients receiving selpercatinib starts overestimating OS compared to the trial data from 2 years onwards. In contrast, the company docetaxel extrapolation appears to underestimate survival from approximately 2 years onwards. The ERG considered (in the ERG report) that the original approach used by the company to model OS was strongly driven by clinical assumptior rather than by actual patient data. This remains the case. Whilst alternative distributions could be chosen to model OS, it is difficult to justify use o any one distribution over another. The distribution that generated a 5-year survival estimate that was closest to estimates provided by clinical exp was the Gompertz distribution (5-year survival of 29.3%). Using the Gompertz distribution to model OS increases the company's ICER per QALY gained for selpercatinib versus docetaxel to [redacted] and versus nintedanib+docetaxel to [redacted]. These results should not be viewed as the ERG's preferred ICERs per QALY gained, rather they should be considered as results that are more plausible than the company ICERs per QALY gaine given the company clinicians' 5-year survival estimates. The ERG has been able to verify the base case deterministic cost effectiveness results presented in Appendix A match those generated by the company TE model. However, the ERG was unable to verify the results of deterministic sensitivity analyses as the ERG was unable to run the macros that generate the deterministic sensitivity analyses in the TE model.
issue 9: gressive disease th state utility value	YES	Eli Lilly and Company acknowledge the ERG's preference to use the health state utility value (HSUV) for progressed disease (PD), which was chosen by the NICE Committee during assessment of TA484 (0.569).[21] As outlined in the Company's original submission (Document B, Section B.3.4.1), European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 data were collected in the LIBRETTO-001 study. Th questionnaire was to be answered by the patient to the best of his/her ability within 7 days of each radiologic assessment, preferably prior to lear the results of the radiologic disease assessment, and at the end of the treatment visit (approximately every 8 weeks).[5] Utility was estimated from the EORTC QLQ-C30 data using mapping algorithms reported by Khan et al. (2016).[22] As outlined in the Company's original submission (Document B, Section B.3.4.2), the beta-binomial and RE linear regression models, provided in the mapping study by Khan e

(2016),[22] were found to offer the best fit to the data, but produced unrealistic baseline utility values (0.9984 and 0.99, respectively). As such, an additional mapping algorithm reported by Young et al. (2015)[23] that maps the EORTC QLQ-C30 to the 3-level EuroQol 5-dimensions questionnai (EQ-5D-3L) has since been explored. The utility estimates from TA484 (Company original base case and ERG preference) and the new mapping algorithm from Young et al. (2015)[23] are summarised in Table 10.

Table 10. Utility estimates for pre-treated NSCLC

Health State	Company Base Case for Original Submission	ERG Preference	LIBRETTO-001 EORTC data mapped to EQ-5D-3L
			Young (2015)[a]
PF	0.713[b]	0.713[c]	[redacted]
PD	0.688[d]	0.569[e]	[redacted]

Footnotes: [a] Using response mapping; [b] ERG preferred estimate in TA484 (Guidance section 4.18; Committee Papers P 550) based on van den Hout 2006 and EQ-5D collected in CheckMate 057; [c] All post-baseline pre-progression assessments; [d] Manufacturers estimate in TA484; [e] The original HSUV of 0.688 used by the manufacture considered too optimistic by the ERG.
Abbreviations: CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-3L: 3-level EuroQol five-dimensions question ERG: Evidence Review Group; NR: not reported; NSCLC: non-small cell lung cancer; PD: progressed disease; PF: progression-free; SD: standard deviation; SE: sta error; TA: technology assessment.
Source: TA484[21] and Eli Lilly and Company Data on File 2020.[5]

The mapping algorithm from the Young et al (2015)[23] study produced a plausible utility value for the progression-free (PF) health state of [redacted] Us this value would adhere more closely with NICE's reference case[24] compared with values from TA484, as it was derived in patients with advance non-squamous *RET* fusion-positive NSCLC (i.e. the target population), as opposed to advanced NSCLC patients without a *RET* fusion.[21] Consequently, a utility value of [redacted] was used for the PF health state in the Company's revised base case economic model. Alternative utility valu were considered as scenario analyses.

The PD health state utility value estimated using the Young et al (2015)[23] mapping algorithm was [redacted]. The Young et al. (2015)[23] PD value excee both the utility value used in the Company's original submission (0.688) and the ERG's preferred value (0.569), which were both derived from TA484. The Young et al. mapped utility value of [redacted] may be considered less plausible due to the low number of EORTC QLQ-C30 observations PD collected from LIBRETTO-001 thus far. However, because advanced NSCLC patients with a *RET* fusion tend to be younger and non-smoker the Company consider that these patients likely have a higher utility value than the general population of advanced NSCLC patients, which may partially explain the higher PD value obtained from the mapping algorithms. Given the low patient numbers informing the mapping process for PD [redacted] was not chosen as the revised value to inform the updated base case analyses. Instead, the mid-point between the ERG's preferred value ar the value chosen in the Company's original submission was therefore selected for the PD health state in the Company's revised base case econo model (i.e. 0.628).

The revised results of Company's cost-effectiveness analysis are presented in Appendix J.

G comment

The NICE recommended approach (as set out in the NICE Reference Case) is that the EQ-5D tool is the preferred measure of health-related qua of life in adults and that a set of preference values elicited from a large UK population study using a choice-based method of valuation should be applied to generate utility values. The utility values used by the company have been generated from EORTC QLQ-C30 data that have been converted into utility values using a mapping algorithm. The company utility values generated using this approach are significantly higher than the EQ-5D utilities accepted by the NICE ACs for TA484 (an appraisal of nivolumab as a treatment option for locally advanced or metastatic non-squamous NSCLC after chemotherapy). The ERG considers that the PFS and PD health state utility values preferred by the NICE AC for TA484 the most relevant values available. Using the NICE AC for TA484 preferred utility values increases the company base case ICER per QALY gain for selpercatinib versus docetaxel to [redacted] and versus nintedanib+docetaxel to [redacted].

issue 10: Costing eatment with ercatinib

YES

Eli Lilly and Company agree with the ERG that patients with PD could continue to receive selpercatinib beyond progression in clinical practice if t clinician deems that they are continuing to derive clinical benefit.[1] Accordingly, in order to capture this, the cost-effectiveness model has been updated with a revised, conservative approach to modelling time-to-treatment discontinuation (TTD). In the updated base case analysis, time on treatment curves were based on PFS, but were adjusted such that patients were assumed to discontinue treatment in the model eight weeks afte PFS event. This was informed by the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial ([redacted] days [IA (Table 11). Treatment discontinuation for comparators was modelled to align with PFS, capped at a maximum number of cycles where specified. updated cost-effectiveness results are presented in Appendix A.

Table 11. Mean time (days) between meeting the PFS endpoint and treatment discontinuation for NSCLC pre-patients in LIBRETTO-001

	Pre-treated NSCLC (IAS) (N=184)
Discontinued treatment during trial follow-up, n (%)	[redacted]
Time between PFS and treatment discontinuation	
Mean (days)	[redacted]
SD	[redacted]
Min, max (days)	[redacted]
95% CI	[redacted]

		Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; NSCLC: non-small cell lung cancer; PFS: progress-free survival; SD: standard deviation. **Source:** Eli Lilly and Company Ltd. Data on File.[5]
G comment		In the original company model, an option was available to model cost of treatment using extrapolated LIBRETTO-001 trial TTD data. This option not available in the company TE model. The ERG notes that the distribution that was the best fit to LIBRETTO-001 TTD data was the exponentia distribution, and modelling TTD using the exponential distribution significantly increased the cost of selpercatinib. The ERG considers that use of exponential distribution is the most accurate approach to estimating the cost of selpercatinib treatment and is disappointed to see that this option now been removed from the company TE model. The ERG preferred approach remains using TTD data from the LIBRETTO-001 trial. Given this is no longer an option in the company TE model, ERG took the exponential distribution fitted to the LIBRETTO-001 trial TTD data from the original company model and used it in the company TE model. This increases the ICER per QALY gained for selpercatinib versus docetaxel to [redacted] and versus nintedanib+docetaxel to [redacted].
issue 11: Cost of ng for *RET* fusions	YES	It is likely that next generation sequencing (NGS) at genetic hubs will become the routine method for conducting molecular genetic testing in the NHS. The use of NGS to identify *RET* gene fusions is considered to be cost-effective, as it allows multiple potentially oncogenic genes to be teste for abnormalities in parallel. Since this approach will be routinely implemented across the UK, Eli Lilly and Company believe that the cost of screening a population of pre-treated non-squamous NSCLC patients for *RET* fusions, to identify which patients will receive selpercatinib, should theoretically not be included in the economic assessment. However, the Company recognise that it is uncertain when NGS within these hubs will be fully operational and a cost specifically attributed to the *RET*-fusion portion of a multi-gene testing NGS panel has therefore been applied in the updated model. A figure of [redacted] per test was recommende NHS England. This figure is based on a prevalence rate for *RET* fusions among NSCLC patients of 1.5% (Sireci et al. 2019),[25] which equates to approximately [redacted] [redacted]/0.015) per *RET* fusion-positive patient identified. This value has been applied in the model. Eli Lilly and Company believ this cost to represent a suitable proxy for testing *RET* among multiple genetic markers in the UK via the genetic hub structure. The updated cost-effectiveness results, which account for the costs associated with *RET* testing, are presented in Appendix A.
G comment		No comment.
issue 12: NICE of Life criteria may be met	YES	As outlined in the Company's response to Issue 8, the mean OS estimate for patients receiving nintedanib plus docetaxel of [redacted], produce using the ERG's preferred modelling methods, is considered to be a substantial overestimate of survival on this treatment. Expert clinical opinion was that patients receiving docetaxel monotherapy alone in the second line would be unlikely to survive for more than 24 months, and survival estimates for docetaxel monotherapy using the ERG's preferred modelling methods were much greater than estimates provided by the expert

stions for clinical erts: What is the ected mean survival eople with RET on-positive anced NSCLC iving second-line motherapy etaxel with or out nintadenib)?

plausible that ercatinib will ease the survival of ple with RET fusion-tive advanced CLC by at least 3 ths compared with etaxel with or out nintadenib?

clinicians. Since the QALY increment for nintedanib plus docetaxel is added to this overestimated docetaxel arm, the ERG's estimate for the nintedanib plus docetaxel arm is also anticipated to be a significant overestimation.[1]

The Company's original survival estimate for nintedanib plus docetaxel (median OS: [redacted] months) and the Company's revised survival estimate ([redacted] months) are similarly considered to be overestimations. As discussed in response to Issue 6, the application of the time acceleration factor adjust for *RET* fusion status, in addition to use of multivariable regression and propensity score matching to adjust for other prognostic factors, resulted in overestimates for OS for the reference arm, and thus nintedanib plus docetaxel, for which hazard ratios from the NMAs were applied.

The Company's revised base case survival outcomes are summarised in Table 12.

Table 12. Revised base case clinical outcomes: PFS and OS

Intervention/comparator	Median PFS (months)	Median OS (months)
Selpercatinib	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]

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

Given the above, *RET* fusion-positive patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second line in the UK are anticipated to have a life expectancy of <24 months and are highly likely to experience an extension to life >3 months if they were to receive selpercatinib monotherapy. Evidence to support the consideration of selpercatinib under the End of Life are summarised in Table 13.

Table 13. End-of-life criteria

Criterion	Data available
1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Yes –** The results of the base case cost-effectiveness analysis (Appendix J) demonstrated that nintedanib plus docetaxel had a predicted survival of [redacted] months and docetaxel monotherapy a predicted survival of [redacted] months. However, as described in Issue 6, the adjustment made to the docetaxel reference arm, through application of the time acceleration factor to adjust for *RET* fusion-positive status and propensity score matching, had resulted in overly optimistic OS estimations for both

	comparators. The median OS of [redacted] months and [redacted] months for nintedanib plus docetaxel and docetaxel monotherapy, respectively, are therefore considered to be overestimations.
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally at least an additional 3 months, compared with current NHS treatment	**Yes** – Base case cost-effectiveness results illustrate that selpercatinib is associated with an increase in survival of [redacted] months and [redacted] months compared to docetaxel and nintedanib plus docetaxel, respectively. This ~[redacted] emphasises the survival benefit of selpercatinib compared with current NHS treatment and exceeds the 3-month additional survival target.

Abbreviations: NHS: National Health Service; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

Targeted literature review: *RET* fusion-positive NSCLC studies

To supplement estimates of likely survival for comparators relevant to selpercatinib, a targeted literature review was conducted to identify studies assessing the efficacy of treatments in advanced *RET* fusion-positive NSCLC (Appendix H, Table 26). Results from the REVEL trial[17] and the LU Lung 1 trial[26] in non-*RET* fusion positive patients are also included in Table 26 for reference.

No studies that assessed the efficacy of relevant comparators to selpercatinib in the UK in pre-treated advanced non-squamous *RET* fusion-posi NSCLC patients were identified. As a result of this, Eli Lilly and Company reviewed the only identified study in *RET* fusion-positive patients asses treatment in a second line population (Drilon 2016).[27] In Drilon 2016, median survival in advanced *RET* fusion-positive NSCLC patients treated in second line and beyond with cabozantinib was 9.0 months. This is significantly lower than Company cost-effectiveness model estimates for eithe docetaxel monotherapy ([redacted] months) or nintedanib plus docetaxel ([redacted] months).[27] Although cabozantinib is not a comparator relevant to the Uk these results show that treatment of advanced *RET* fusion-positive patients with a broad-acting MKI, similar to nintedanib, results in a survival estimate well under two years.

Further evidence in advanced *RET* fusion-positive patients was identified in a mixture of first- and second-line patients in Shen 2020.[28] Shen 202 reported a median OS of 22.6 months in 10 advanced *RET* fusion-positive NSCLC patients that had never received pemetrexed-based chemotherapy, and 35.2 months in 28 patients that had received pemetrexed-based chemotherapy.[28] Although estimates for patients that had received pemetrexed-based chemotherapy exceeded two years, OS was measured from the date of confirmed Stage IIIa/IV disease, which prolonged survival estimates compared with Company estimates.[28] In addition, the study was completed in China, which has different treatment patterns and patient characteristics to the UK.[28]

		Further evidence in advanced *RET* fusion-positive patients was identified in a population of first line patients.[29] Gautschi 2017 reported a median of 24.8 months in 70 *RET* fusion-positive NSCLC patients treated with platinum-based chemotherapy and 23.6 months in 57 *RET* fusion-positive patients treated with pemetrexed plus a platinum agent.[29] If estimates of survival for first-line non-targeted therapy in *RET* fusion-positive patients close to or less than 24 months, it is deemed highly unlikely that survival in second line with non-targeted therapies such as docetaxel and ninted plus docetaxel would be greater than 24 months. This again would suggest that the estimated median OS from the Company's cost-effectiveness model (as well as the ERG's estimates) for patients receiving docetaxel monotherapy and nintedanib plus docetaxel in the second line is an overestimation. Finally, median OS trial data for non-*RET* fusion positive patients receiving docetaxel monotherapy (REVEL: 9.1 months)[17] and nintedanib plus docetaxel (LUME-Lung 1: 12.6 months)[26] is also significantly less than 24 months. Although positive *RET* fusion status has been associated with favourable OS compared with patients without a *RET* fusion,[18] it is considered highly unlikely that this would extend life beyond 24 months for eit treatment. Furthermore, even with the highly optimistic estimations from the Company model for the comparators, there is still a survival benefit c greater than 3-months between selpercatinib and relevant UK comparators. Given the above analysis, Eli Lilly and Company believe that: • The ERG's 5-year survival projection of [redacted] (original Company model), or [redacted] (revised Company model) for pre-treated advanced squamous and *RET* fusion-positive NSCLC patients treated with docetaxel monotherapy does not align with expert clinical opinion and is l to be highly optimistic. As such, the ERG's mean OS estimate of [redacted] using the Company's original model for patients treated nintedanib plus docetaxel is likely to be an overestimate and does not align with expert clinical opinion or the published literature. Furtherm this estimate converges with the Company mean life-year estimate predicted by the model for selpercatinib ([redacted]), which is considered to be clinically plausible, given the treatment effects estimated by the Company's revised NMA and that selpercatinib specifi targets the oncogenic driver of the patient's cancer. • The Company considers that its cost-effectiveness model OS estimates for comparators to selpercatinib are more accurate than the ER but likely remain overly optimistic when compared with expert clinical opinion and considering published survival outcomes for the advar *RET* fusion-positive patients receiving non-targeted therapies in the first line and second line setting • Pre-treated advanced *RET* fusion-positive NSCLC patients receiving docetaxel monotherapy or nintedanib plus docetaxel in the second in the UK have a life expectancy of <24 months and are highly likely to experience an extension to life >3 months if they were to rec selpercatinib monotherapy, therefore meeting both end-of-life criteria

G comment		The ERG considers that the evidence presented by the company indicates that it is plausible that life expectancy for patients with *RET* fusion positive disease who have been treated in the second-line setting extends beyond 2 years. Whilst results from the company model suggest that t OS gain for patients receiving selpercatinib could exceed 3 months, without more robust comparative OS data this gain is highly uncertain.
issue 13: Absence ata for subgroups of ents listed in the scope issued by E **stion for clinical erts:** Do you agree company tioning of ercatinib in non-amous disease?	NO	Eli Lilly and Company agree with the clinical advice provided to the ERG that it was reasonable to exclude patients with advanced squamous cell NSCLC, because *RET* fusions are extremely rare in this population.[6]
G comment		No comment.

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Appendix A

Summary of changes to the company's cost-effectiveness estimate(s)

Following feedback from the ERG, Eli Lilly and Company have updated the economic model to produce a revised base case. The revised cost-effectiveness model, fully annotated to highlight updates made since the original submission, is provided alongside this document. A summary of the updates made to inform the revised base case of the model is presented in Table 14 below. Please note that given the short timeframe associated with the Technical Engagement and the significant updates required to the economic model, it was not possible for Eli Lilly and Company to provide updated base case ICERs for each change made to the economic model.

The LIBRETTO-001 data from the 30th March 2020 data cut off, presented in response to Issue 2, represent a larger sample size and longer duration of follow up. As illustrated in the response to Issue 2, similar results were observed for PFS and OS between the 30th March 2020 and 19th December 2019 data cut. Whilst these data corroborate and therefore provide additional confidence in the results of the 19th December 2019 data cut, they have not been used to conduct the ITC, nor to inform the revised base case economic model, due to time constraints and as only a small number of additional events had occurred by the later data cut. For the reasons described above, these data would have minimal impact on the cost-effectiveness results.

A summary of the results from the revised base case model are available in Table 15. Full updated model results are available in Appendix J.

Table 14. Summary of changes to the revised base case cost-effectiveness model

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement
Key issue 4: Relevant comparator treatments	All patients: • Nintedanib + docetaxel • Atezolizumab PD-L1≥1%: • Nivolumab • Pembrolizumab	All patients: • Nintedanib + docetaxel • Docetaxel monotherapy

Key issue 5: The relevance of populations participating in the trials that provided comparator evidence for the company NMAs	NMA model selection (PFS and OS): Fixed effects hierarchical exchangeable model adjusted for age (centered on 61 years of age)	NMA model selection (PFS and OS): Fixed effects hierarchical exchangeable model
Key issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis	Approach to generating and adjusting the pseudo-control arm for LIBRETTO-001: • Adjust REVEL IPD for prognostic impact of *RET* fusion-positive status using Flatiron data • Adjustment for further prognostic factors using TMLE	Approach to generating and adjusting the pseudo-control arm for LIBRETTO-001: • Adjust REVEL IPD for prognostic impact of *RET* fusion-positive status using Flatiron data • Adjustment for further prognostic factors using propensity score matching
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Key issue 8:** The company modelling of survival for patients receiving nintedanib + docetaxel	PFS extrapolation: Stratified gamma	PFS extrapolation: Stratified Gompertz (updated based on revised NMA approach and further clinical input)
Key issue 7: The company modelling of survival for patients receiving selpercatinib **Key issue 8:** The company modelling of survival for patients receiving nintedanib + docetaxel	OS extrapolation: Unstratified exponential	OS extrapolation: Spline/Knot=1 (updated based on revised NMA approach and further clinical input)
Key issue 9: Progressed disease health state utility value	PF: 0.713 (TA484)[21] PD: 0.688 (TA484)[21]	PF: [redacted] (LIBRETTO-001; EORTC-QLQ-C30 mapped to EQ-5D-3L using Young et al [2015])[23] PD: 0.628 (intermediate between the ERG preferred value [0.569] and the company's original PD utility value [0.688])
Key issue 10: Costing of treatment with selpercatinib	Time to treatment discontinuation: assumed TTD was equivalent to PFS	Time to treatment discontinuation: TTD curves were based on PFS but the selpercatinib TTD curve was shifted to account for the mean time from progression to treatment discontinuation observed in the LIBRETTO-001 trial
Key issue 11: Cost of testing for *RET* fusions	The cost of *RET* testing not included	Cost specifically attributed to the *RET*-fusion portion of a multi-gene testing NGS panel included in the model
Additional change 1	No PAS applied	A simple PAS, representing a [redacted] discount, has been approved for selpercatinib by PASLU and has been applied to the model

		Further details are available in Appendix
Additional change 2	Selpercatinib acquisition costs: List price of a 60-capsule bottle of 80 mg or 40 mg: £[redacted]	Selpercatinib acquisition costs: List price 60 capsule bottle of 80 mg: £4,680.00 60 capsule bottle and 40 mg: £2,340.00 Selpercatinib acquisition costs: Price (with proposed PAS discount applied) 60 capsule bottle of 80 mg: £[redacted] 60 capsule bottle and 40 mg: £[redacted] Further details are available in Appendix I
Additional change 3	ECG costs: ECG costs applied to intervention and comparators in health state costs	ECG costs: One-off cost of seven ECGs is included in the model for selpercatinib only based on final SmPC[30] Further details are available in Appendix I
Additional change 4	Selpercatinib dose reductions: The mean dose intensity in the LIBRETTO-001 trial ([redacted]) was used to account for dose reductions and any treatment breaks	Selpercatinib dose reductions: Proportions of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the LIBRETTO-001 trial Further details are available in Appendix I

Abbreviations: FE: fixed effects; IPD: individual patient data; ECG: electrocardiogram; NGS: next-generation sequencing; NMA: network meta-analysis; OS: overall survival; PAS: patient access scheme; PASLU: patient access scheme liaison unit; PD-L1: programmed death ligand 1; PFS: progression-free survival; *RET*: rearranged during transfection: SmPC: Summary of Product Characteristics; TMLE: targeted minimum loss-based estimation; TTD: time-to-treatment discontinuation.

Updated base case cost-effectiveness results

Table 15. Revised base case cost-effectiveness model results for *RET* fusion-positive NSCLC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,833
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	104,016[a]	69,411
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,833	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-year.

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Appendix B

Issue 2: LIBRETTO-001 Trial Survival Events and Length of Follow-Up

Efficacy data from 30th March 2020

Efficacy data for the entire IAS efficacy population (N=218) as of the 30th March 2020 are presented in full below.

ORR by RECIST v1.1 (primary endpoint)

Table 16. BOR, ORR and CBR by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

Status	IAS N=218
BOR (n, %)[a]	
CR	9 (4.1)
PR	115 (52.8)
SD	81 (37.2)
SD*[,b]	60 (27.5)
PD	5 (2.3)
NE	8 (3.7)
ORR (CR+PR)[c,d]	
Number of patients (n, %)	124 (56.9)
95% CI	50.0–63.6
CBR (CR+PR+SD*)[d,e]	
Number of patients (n, %)	184 (84.4)
95% CI	78.9–89.0

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] stable disease lasting 16 weeks or more; [c] objective response rate is defined as the proportion of patients with best overall response of confirmed CR or PR; [d] 95% confidence intervals calculated using Clopper-Pearson method; [e] Clinical benefit rate is defined as the proportion of patients with best overall response of confirmed CR, PR or stable disease lasting 16 or more weeks (SD*). Stable disease was measured from the date of first dose of selpercatinib until the criteria for disease progression was first met.

Abbreviations: BOR: best overall response; CBR: clinical benefit rate; CI: confidence interval; CR: complete response; IAS: Integrated Analysis Set; IRC: Independent Review Committee; NE: not estimable; NSCLC: non-small cell lung cancer; ORR: objective response rate; PD: progressive disease; PR: partial response; *RET:* rearranged during transfection; SD: stable disease.

Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

DOR (secondary endpoint)

Table 17. DOR by IRC with confirmed CR or PR for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

Status	IAS N=218
Patients with best response of confirmed CR or PR[a]	124
Response states (n, %)[b]	
Disease progression	34 (27.4)
Died (no disease progression beforehand)	4 (3.2)
Censored	86 (69.4)
Reason censored (n, %)	
Alive without documented disease progression	83 (66.9)
Subsequent anti-cancer therapy of cancer related surgery without documented PD	3 (2.4)
Duration of response (n, %)	
<6 months	36 (29.0)
≥6 to 12 months	51 (41.4)
≥12 to 18 months	29 (23.4)
≥18 to 24 months	5 (4.0)
≥24 months	3 (2.4)
Duration of response (months)[c,d]	
Median	17.51
95% CI	12.1–NE
Minimum, maximum	1.8+, 29.8+
Duration of follow-up (months)[c]	
Median	11.99
25th, 75th percentiles	7.4, 15.9
Rate (%) of DOR[c,e]	
6 months or more	85.8
95% CI	77.9, 91.1
12 months or more	69.1
95% CI	58.1, 77.8

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] Status as of the patients last disease assessment on or before cut-off date; [c] Estimated based on Kaplan-Meier methods. NE = not estimable/ + = censored observation; [d] 95% confidence interval was calculated using Brookmeyer and Crowley method; [e] 95% confidence interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; CR: complete response; DOR: duration of response; IAS: Integrated Analysis Set; IRC: independent review committee; PAS: Primary Analysis Set; NE: not estimable; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

PFS (secondary endpoint)

Table 18. PFS by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

	IAS N=218
Status (n, %)[a]	
Disease progression	74 (33.9)
Censored	144 (66.1)
Duration of PFS (months)[b]	
Median	19.29
95% CI	16.5–NE
Minimum, maximum	0.0+, 30.6+
Duration of follow-up (months)	
Median	13.60
25th, 75th percentiles	9.0, 16.6
Rate (%) of PFS[b,c]	
6 months or more	84.4
95% CI	78.7–88.7
12 months or more	69.7
95% CI	62.2–75.9
18 months or more	54.2
95% CI	44.4–63.1
24 months or more	43.7
95% CI	31.5–55.4

Footnotes: [a] Based on IRC assessment using RECIST (versions 1.1); [b] Estimated based on Kaplan-Meier methods. NE = not estimable/ + = censored observation; [c] 95% confidence interval was calculated using Brookmeyer and Crowley method.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: independent review committee; NE: not estimable; NSCLC: non-small cell lung cancer; PAS: Primary Analysis Set; PFS: progression-free survival; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

[redacted]

Figure 5. Kaplan-Meier plot of PFS for second line (IAS) *RET*-fusion positive NSCLC patients (30th March 2020 data cut; IRC)

Abbreviations: IAS: Integrated Analysis Set; IRC: Independent Review Committee; NSCLC: non-small cell lung cancer; PFS: progression-free survival; *RET*: rearranged during transfection.

OS (secondary endpoint)

Table 19. OS by IRC for *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (30th March 2020 data cut)

	IAS N=218
Status (n, %)[a]	
Died	41 (18.8)
Censored	177 (81.2)
Duration of OS (months)[b,c]	
Median	NE
95% CI	25.7–NE
Minimum, maximum	0.3, 34.5+
Duration of follow-up (months)	
Median	14.26
25th, 75th percentile	10.1, 19.5
Rate (%) of OS[b,c]	
6 months or more	95.4
95% CI	91.6–97.5
12 months or more	88.1
95% CI	82.5–91.9
18 months or more	77.6
95% CI	69.4–83.9
24 months or more	67.3
95% CI	55.4–76.7

Footnotes: [a] Status as of the last contact on or before the 30th March 2020; [b] Estimate based on Kaplan-Meier method. NE = not estimable/ + = censored observation; [c] 95% confidence interval was calculated using Brookmeyer and Crowley method.
Abbreviations: CI: confidence interval; IAS: Integrated Analysis Set; IRC: independent review committee; NE: not estimable; NSCLC: non-small cell lung cancer; OS: overall survival; PAS: Primary Analysis Set; *RET*: rearranged during transfection.
Source: Eli Lilly Data on File (30th March 2020 data cut-off).[5]

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Figure 6. Kaplan-Meier plot of OS for second line (IAS) *RET*-fusion positive NSCLC patients (30th March 2020 data cut; IRC)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; IRC: Independent Review Committee; NA: not applicable; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

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Appendix C

Issue 3: Prior Treatments Received by the LIBRETTO-001 Trial Population Do Not Reflect NHS Clinical Practice

Breakdown of prior treatments in LIBRETTO-001

A detailed breakdown of the prior treatments received by patients in the IAS analysis set is presented in Table 20. Kaplan-Meier plots of PFS and OS for the IAS MKI-naïve subgroup are provided below in Figure 7 and Figure 8, respectively.

Table 20. Prior treatments received by the IAS analysis set in LIBRETTO-00

Characteristic	IAS N=184
Received prior systemic therapy n (%)	
Yes	184 (100.0)
No	0 (0.0)
Prior systemic regimens n (%)	
0	0 (0.0)
1-2	100 (54.3)
3 or more	84 (45.7)
Number of prior systemic regimens n	
Mean (SD)	[redacted]
Median (range)	[redacted]
Type of prior systemic therapy n (%)	
MKI	67 (36.4)
Cabozantinib	[redacted]
Vandetanib	[redacted]
Sorafenib	[redacted]
Lenvatinib	[redacted]
Other MKIs	[redacted]
Chemotherapy	184 (100.0)
Platinum Chemotherapy	184 (100.0)
Radioactive Iodine	[redacted]
Anti-PD1/PD-L1 Therapy	100 (54.3)
Selective *RET* Inhibitor	[redacted]
Taxane Chemotherapy	[redacted]
Other Systemic Therapy	[redacted]

Footnotes: Patients may be counted in more than one row of type of prior systemic therapy. 16th December data-cut
Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; PD1: programmed cell death protein 1; PD-L1: programmed death ligand 1; *RET*: rearranged during transfection; SD: standard deviation.

Figure 7. Kaplan-Meier plot of PFS by Independent Assessor for second line (IAS) *RET*-fusion positive NSCLC patients without prior MKI treatment (30th March 2020 data cut)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; NSCLC: non-small cell lung cancer; PFS: progression-free survival; *RET*: rearranged during transfection.

Figure 8. Kaplan-Meier plot of OS by Independent Assessor for second line (IAS) *RET*-fusion positive NSCLC patients without prior MKI treatment (30th March 2020 data cut)

[redacted]

Abbreviations: IAS: Integrated Analysis Set; MKI: multi-kinase inhibitor; NA: not applicable; NSCLC: non-small cell lung cancer; OS: overall survival; *RET*: rearranged during transfection.

Appendix D

Issue 5: Relevance of the population participating in the trials that provided comparator evidence for the Company NMAs

The DIC values for key covariates informing the NMA meta-regression are provided in Table 21.

Table 21. DIC statistics for OS, PFS and ORR based on either fixed or random effects models with individual covariates

Covariate	DIC		
	OS	PFS	ORR
FE – no covariates	[redacted]	[redacted]	[redacted]
RE – no covariates	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model + age	[redacted]	[redacted]	[redacted]
FE – hierarchical exchangeable model + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + age	[redacted]	[redacted]	[redacted]
FE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
FE + ECOG	[redacted]	[redacted]	[redacted]
FE + proportion of male participants	[redacted]	[redacted]	[redacted]
RE + age	[redacted]	[redacted]	[redacted]
RE + proportion of Asian participants	[redacted]	[redacted]	[redacted]
RE + ECOG	[redacted]	[redacted]	[redacted]
RE + proportion of male participants	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: deviance information criterion; ECOG: Eastern Cooperative Oncology Group; FE: fixed effects; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RE: random effects.

[a] The hierarchical exchangeable structure was applied only to the model that was found to have the lowest DIC values with covariate adjustments. Hence, the DIC value for fixed effects hierarchical exchangeable model with age is available for OS and PFS while the DIC value for fixed effect hierarchical exchangeable model with Asian participants is available for ORR.

[b] models with convergent issues.

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Appendix E

Issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis

Programming language for propensity score matching

The R programme code, used for the Flatiron adjustment for *RET*-status was provided in the original submission (Appendices, Section D.1.8). Code for the propensity score matching approach is provided in Table 22.

Table 22. Programme code used in the propensity score matching

Function	Programme	Code
Estimation of treatment effect		
Pilot *RET* fusion adjusted chart	R	[redacted]
Propensity score matching	R	[redacted]

		[redacted]
Propensity score matching using a generalised boosted model	R	[redacted]

		[redacted]

Code for NMA of English second line treatments

OPENBUGS codes were translated into JAGS as the background model code in BATMAN; the programme used to conduct the second line NMA. In this section the JAGS code used in the NMA of English second line treatments for NSCLC are presented.

Figure 9. JAGS code for ORR in the second line NMA (fixed effects plus hierarchical exchange adjusted for the proportion of Asian patients)

[redacted]

Abbreviations: NMA: network meta-analysis; ORR: objective response rate.

Figure 10. JAGS code for PFS in the second line NMA (fixed effects plus hierarchical exchange)

[redacted]

Abbreviations: NMA: network meta-analysis; PFS: progression-free survival.

Figure 11. JAGS code for OS in the second line NMA (fixed effects plus hierarchical exchange)

[redacted]

Abbreviations: NMA: network meta-analysis; OS: overall survival.

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Appendix F

Issue 6: Uncertainty associated with the pseudo-control (reference) arm used to connect selpercatinib for network meta-analysis

LIBRETTO-001 and REVEL patient characteristic data pre- and post-adjustment for *RET* fusion status and other prognostic factors

Table 23. Summary of patient characteristics of the REVEL and LIBRETTO pre-treated NSCLC trial populations, before and after adjustment for *RET* fusion status and the propensity score matching process

Characteristic	Baseline characteristics		After *RET* adjustment Before propensity score matching		After propensity score matching[a]
	LIBRETTO-001, IAS (selpercatinib) (N=184)	REVEL (docetaxel + placebo) (N=447)[b]	Selpercatinib arm (N=174)[c]	Docetaxel + placebo arm (N=447)	Docetaxel + placebo arms (N=174)
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology: Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≥ 1, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis to start of trial (median months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] The analysis followed greedy match as the matching algorithm. [b] A subgroup of the REVEL trial comprised of patients with non-squamous NSCLC was used to generate the pseudo-control arm. [c] The baseline characteristics of the selpercatinib arm after *RET* adjustment do not fully align with the IAS from LIBRETTO-001 due to the need to exclude a small number of patients (n=10) from the IAS to inform the propensity score matching process. This was due to these patients having missing data on covariates required for the matching process.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS, Integrated Analysis Set (all patients treated with platinum-based chemotherapy); NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.

Source: Eli Lilly and Company Ltd. Data on File.(7)

Updated NMA results

The results of the NMA using the propensity score matching approach, which provide comparative efficacy for selpercatinib and relevant comparators in the UK, are reported in the sections that follow. Treatment effects are presented versus the common comparator in the network, docetaxel.

ORR by RECIST v1.1 (primary endpoint)

The relative treatment effects using the FE model (hierarchical exchangeable and adjusted for the proportion of Asian patients) for interventions of interest for ORR versus docetaxel are presented in Table 23 and the forest plot is presented in **Error! Reference source not found.**. Relative to nintedanib plus docetaxel, selpercatinib demonstrated higher odds of inducing an ORR compared to docetaxel plus placebo (ORR: [redacted]; 95% CrI: [redacted]).

Table 23. Relative treatment effects expressed as odds ratios versus docetaxel (with 95% CrI) for ORR in second line advanced NSCLC patients

Treatment	Median OR (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Footnotes: [a] Fixed hierarchical exchangeable model adjusted for the proportion of Asian patients.
Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[5]

[redacted]

Figure 12. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for ORR in second line advanced NSCLC patients (fixed effects hierarchical exchangeable adjusted for Asian patients)

Abbreviations: CrI: Credible interval; NSCLC: non-small cell lung cancer; ORR: objective response rate.
Source: Eli Lilly and Company Ltd. Data on File.[5]

PFS (secondary endpoint)

The relative treatment effects for interventions of interest for PFS versus docetaxel are presented in Table 24, using the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 13. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of disease progression compared to docetaxel (hazard ratio: [redacted] CrI: [redacted]).

Table 24. Relative treatment effects expressed as hazard ratios versus docetaxel plus placebo (with 95% CrI) for PFS in second line advanced NSCLC patients

Treatment	Median hazard ratio (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Figure 13. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for PFS in second line advanced NSCLC patients (fixed effects hierarchical exchangeable)

[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

OS (secondary endpoint)

The relative treatment effects for interventions of interest for OS versus docetaxel plus placebo are presented in Table 25, for the FE (hierarchical exchangeable) model. The forest plot is presented in Figure 14. Relative to nintedanib plus docetaxel, selpercatinib demonstrated a lower risk of death compared to docetaxel (hazard ratio: [redacted] 95% CrI: [redacted]).

Table 25. Relative treatment effects expressed as hazard ratios versus docetaxel plus placebo (with 95% CrI) for OS in second line advanced NSCLC patients

Treatment	Median hazard ratio (95% CrI) versus docetaxel + placebo
Fixed effects (hierarchical exchangeable)	
Selpercatinib	[redacted]
Nintedanib + docetaxel	[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Figure 14. Forest plot of relative treatment effects for selpercatinib and relevant comparator intervention versus docetaxel for OS in second line advanced NSCLC patients (fixed effects hierarchical exchangeable)

[redacted]

Abbreviations: CrI: credible interval; NSCLC: non-small cell lung cancer; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on File.[5]

Appendix G

Issues 7 and 8: Survival extrapolations for selpercatinib and comparators

PFS

Long-term extrapolations for PFS are provided below in Figure 15 and Figure 16.

Figure 15. Selpercatinib PFS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

Figure 16. Reference arm (docetaxel) PFS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

OS

Long-term extrapolations for OS are provided below in Figure 17 and Figure 18.

Figure 17. Selpercatinib OS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

Figure 18. Reference arm (docetaxel) OS parametric survival function extrapolations in second line advanced NSCLC patients

[redacted]

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

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Appendix H

Issue 12: NICE End of Life Criteria may not be met

The survival estimates from studies assessing the efficacy and effectiveness of treatments in advanced *RET* fusion-positive NSCLC identified in a targeted literature review are presented in Table 26. Results from the REVEL trial[17] and the LUME-Lung 1 trial[26] in non-*RET* fusion positive patients are also included in Table 26 for reference.

Table 26. Summary of survival estimates in advanced[a] NSCLC patients with or without *RET* fusions treated in the first and second line

Treatment (Source)	RWE mOS	Trial mOS	Predicted mOS (model)
Second line non-*RET* fusion positive NSCLC patients			
Docetaxel (REVEL)[17]	-	9.1	-
Nintedanib + docetaxel (LUME-Lung 1)[26]	-	12.6	-
Second line *RET* fusion-positive patients			
Selpercatinib (LIBRETTO-001 [IAS]; N=184 and Company cost-effectiveness model estimate)[5]	-	[redacted]	[redacted]
Docetaxel (Company cost-effectiveness model estimate)[5]	-	-	[redacted]
Nintedanib + docetaxel (Company cost-effectiveness model estimate)[5]	-	-	[redacted]
Cabozantinib (Drilon 2016[a]; 1 prior line; N=12)[27]	-	9.2	-
Cabozantinib (Drilon 2016[a]; >1 prior line; N=7)[27]	-	9.0	-
First line and second line *RET* fusion-positive patients			
Ever received pemetrexed-based chemotherapy (Shen 2020; N=28)[28]	35.2	-	-
Never received pemetrexed-based chemotherapy (Shen 2020; N=10)[28]	22.6	-	-

Received selective *RET* TKI (Tan 2020; N=35)[20]	49.3	-	-
Selective *RET* TKI naïve (Tan 2020; N=25)[20]	15.3	-	-
First line *RET* fusion-positive patients			
Cabozantinib (Drilon 2016[a]; N=6)[27]	NE	-	-
Platinum based chemotherapy (Gautschi 2017; N=70)[29]	24.8	-	-
Pemetrexed + platinum agent (Gautschi 2017; N=57)[29]	23.6	-	-

Footnotes: [a] All studies summarised in Table 26 reported data in advanced (Stages IIIb or IV) NSCLC except Gautschi 2017. In Gautschi 2017, 78% of patients were Stage IV.
Abbreviations: mOS; median overall survival; mPFS: median progression-free survival; NE: not estimable; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; RWE: real world evidence.

Appendix I

Selpercatinib acquisition costs and dose reductions

As noted in Appendix A, the list prices for selpercatinib formulations (60 capsule bottle of 80 mg or 40 mg selpercatinib) have been updated. In addition, a patient access scheme (PAS) has been approved for selpercatinib, representing a simple discount of [redacted] to the list price. Table 27 presents the drug acquisition costs for selpercatinib based on its current PAS price, licensed dose and modelled dose reductions.

To account for selpercatinib dose reductions (in line with dose reductions recommended in the selpercatinib Summary of Product Characteristics [SmPC]),[30] a proportion of patients were assumed to receive a reduced dose level of 120 mg, 80 mg, or 40 mg orally twice daily, based on the proportions of patients who experienced dose reductions in the IAS population of the LIBRETTO-001 trial. The starting doses in the model are provided in Table 28. Following the first cycle, dose reductions for selpercatinib observed in the IAS population of LIBRETTO-001 were applied to calculate the subsequent acquisition cost per four-week period for selpercatinib. The application of dose reductions was performed in this way on the assumption that most patients receiving selpercatinib will experience adverse events (AEs) in the first treatment cycle. The distribution of dose reductions from LIBRETTO-001 applied after the first cycle is presented in Table 29.

ECG costs of monitoring

Due to QT prolongation reported in some patients receiving selpercatinib, the SmPC recommends that the QT interval be monitored more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.[30] Accordingly, the cost of 7 ECGs (one at baseline and once a month thereafter for 6 months) is included in the model in the selpercatinib arm as a one-off cost and removed from the resource use of comparators.

Table 27. 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	
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 28: Weighted drug acquisition costs for selpercatinib in treatment cycle 1 (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, NSCLC	Total cost per treatment cycle, NSCLC
160 mg, twice daily	[redacted]	[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.
Source: Eli Lilly and Company. Data on file.[5]

Table 29: Weighted drug acquisition costs for selpercatinib in treatment cycles 2+ (including dose reductions)

Dose	Costs per treatment cycle	Proportion of patients on each dose, NSCLC	Total cost per treatment cycle, NSCLC
160 mg, twice daily	[redacted]	[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.
Source: Eli Lilly and Company. Data on file.[5]

Appendix J

Revised base-case cost-effectiveness results

A summary of the results in the revised company base case analysis for *RET* fusion-positive NSCLC, using LIBRETTO-001 data from the 16th December 2019 data cut, is presented below.

Base case results

A summary of the base case analysis results (with PAS) is presented in Table 30. The results illustrate that versus all comparators, selpercatinib is associated with greater QALYs, reflecting the high levels of efficacy of selpercatinib in the second line *RET* fusion-positive NSCLC population.

Table 30. Base-case results for second line *RET* fusion-positive NSCLC: selpercatinib PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,833
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	104,016[a]	69,411
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,833	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET*: rearranged during transfection.

Probabilistic sensitivity analysis (PSA)

The probabilistic base case results are presented in Table 31. The PSA results illustrate that versus both comparators, selpercatinib is associated with greater QALYs. The deterministic and probabilistic base case results are observed to be in close alignment.

Table 31. Probabilistic base-case results second line *RET* fusion-positive NSCLC: selpercatinib PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER pairwise selpercatinib vs comparator (£/QALY)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	74,809
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,775	69,220
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,809	-

Footnotes: [a] Nintedanib plus docetaxel is extendedly dominated.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NSCLC: non-small cell lung cancer; PAS: patient access scheme; QALYs: quality-adjusted life years; *RET:* rearranged during transfection.

The probabilistic cost-effectiveness planes and cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel are presented in

[redacted]

Figure 19.[redacted]

[redacted]

Figure 19. Probabilistic cost-effectiveness plane and cost-effectiveness acceptability curves for selpercatinib vs. docetaxel monotherapy and nintedanib plus docetaxel

Abbreviations: NSCLC: non-small cell lung cancer; QALY: quality-adjusted life year.

Deterministic sensitivity analysis (DSA)

[redacted]

The tornado diagrams for selpercatinib versus docetaxel and nintedanib plus docetaxel are presented in Figure 20 and Figure 21, respectively. The top 25 most influential parameters on the base case are presented in each case.

Figure 20. DSA tornado diagram for selpercatinib versus docetaxel monotherapy

[redacted]

Figure 21. DSA tornado diagram for selpercatinib vs nintedanib plus docetaxel

[redacted]

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Scenario analysis

A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table 32. It should be noted that for scenarios applied to the OS and PFS curves, unless otherwise noted, the specified parametric function is applied to both selpercatinib and all comparator arms.

Table 32. Scenario analysis results for selpercatinib versus relevant comparators

Scenario		Pairwise ICER vs. docetaxel	% ICER change	Pairwise ICER vs. nintedanib + docetaxel	% ICER change
	Base case	**£74,833**	**-**	**£69,411**	**-**
1	Utilities, ERG preferred PD value PF: [redacted] PD: 0.569	£77,331	3.34%	£71,495	3.00%

2	Utilities, All pre-progression observations for PF value PF=[redacted] PD=0.628	£76,111	1.71%	£70,660	1.80%
2	Relative dose intensity applied to selpercatinib	£77,454	3.50%	£72,520	4.48%
8	No diagnostic testing costs	£73,377	-1.95%	£67,685	-2.49%
9	TTD equal to PFS curve	£70,517	-5.77%	£64,293	-7.37%
10	Curve choice: OS – Exponential	£59,398	-20.63%	£54,924	-20.87%
11	Curve choice: OS – Weibull	£71,282	-4.75%	£66,044	-4.85%
12	Curve choice: OS – stratified Weibull	£79,456	6.18%	£75,438	8.68%
13	Curve choice: OS – stratified Gamma (selpercatinib and docetaxel arms only)[a]	£70,644	-5.60%	£62,398	-10.10%
14	Curve choice: PFS – Gompertz	£74,236	-0.80%	£68,677	-1.06%
15	Curve choice: PFS – Gamma (selpercatinib and docetaxel arms only)[a]	£79,152	5.77%	£74,625	7.51%
16	Curve choice: PFS – stratified Weibull	£78,961	5.52%	£74,384	7.16%
17	Curve choice: PFS – spline knot 1	£84,462	12.87%	£80,694	16.26%

Footnotes: [a] AFT models were only applied to the selpercatinib and reference arms, whilst base case extrapolations were utilised for nintedanib plus docetaxel so that the hazard ratio from the NMA could be applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity; TA: technology appraisal.

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