Single Technology Appraisal

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (MA review of TA760) [ID6293]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (MA review of TA760) [ID6293]

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**

3. **Systemic Anti-cancer Therapy (SACT) report**

4. **Expert statement by Clinical Expert – Yvonne Summers – nominated by Eli Lilly**

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

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

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 previously treated *RET* fusion-positive advanced non-small cell lung cancer

[ID6293]

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BID	Twice daily
BIM	Budget impact model
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
CBR	Clinical benefit rate
CDF	Cancer Drug's Fund
CEA	Carcinoembryonic antigen
CGDB	Clinico-Genomics Database
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CrI	Credible interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DIC	Deviance information criterion
DLT	Dose limiting toxicity

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor
eMIT	Electronic market information tool
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of treatment
EQ-5D-3/5L	Euro-QoL Questionnaire 5 Dimensions 3/5 levels
ERG	Evidence review group
FISH	Fluorescence in situ hybridization
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health-state utility value
HTA	Health technology assessment
IAS	Integrated analysis set
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IQR	Interquartile range
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
JAK	Janus kinase
KM	Kaplan-Meier
LPS	Lansky performance score
LTFU	Long term follow-up
LYG	Life years gained
MAPK	Mitogen-activated protein kinase
MHRA	Medicines and Healthcare Regulatory Agency
MKI	Multi-kinase inhibitor
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
MVH	Measurement and Valuation of Health study
NA	Not applicable
NCI	National Cancer Institute
NE	Not estimable
NGS	Next generation sequencing

Abbreviation	Definition
NHS	National Health Service
NHSE	National Health Service England
NHSRC	National Health Systems Resource Centre
NICE	National Institute for Health and care Excellence
NMA	Network meta-analysis
NMD	Non-measurable disease
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tropomyosin receptor kinase
ORR	Objective response rate
OS	Overall survival
OSAS	Overall safety analysis set
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Progressed disease
PF	Progression free
PFS	Progression free survival
PI3K	Phosphoinositide 3-kinase
PPI	Proton pump inhibitors
PPS	Post progression survival
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAI	Radioactive iodine therapy
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RP2D	Recommended phase 2 dose
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCHARR	Sheffield Centre for Health and Related Research
SFU	Safety follow-up
SLR	Systematic literature review

Abbreviation	Definition
SmPC	Summary of Product Characteristics
SOC	Standard of care
SRC	Safety review committee
STA	Single technology appraisal
STAT	Signal transducer and activator of transcription
TA	Technology appraisal
TEAE	Treatment-emergent adverse events
TSD	Technical Support Document
TTD	Time to treatment discontinuation
WTP	Willingness to pay

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

B.1.1 Decision problem

The objective of this submission is to demonstrate the clinical and cost-effectiveness of selpercatinib (Retsevmo®) for adults with previously-treated advanced rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC). Selpercatinib has already received a NICE recommendation for use in the first line (treatment-naïve) patient population via the Cancer Drugs Fund (CDF),[1] so this submission concerns the use of selpercatinib in previously-treated patients.

As this technology was previously made available for *RET* fusion-positive NSCLC in the second line patient population via the CDF (TA760), Eli Lilly and Company aim to address some of the uncertainty associated with this prior submission through the provision of longer-term survival data from a larger patient population from the pivotal LIBRETTO-001 trial.[2]

The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with *RET* fusion-positive advanced non-small cell lung cancer (NSCLC) that has been previously treated but has not been treated with a RET inhibitor.	Adults with previously treated advanced, non-squamous, *RET* fusion-positive NSCLC who require systemic therapy but who have not been previously treated with a RET inhibitor.	*RET* fusions rarely occur in NSCLC tumours with squamous histology, which was acknowledged by the Committee in a previous NICE appraisal of selpercatinib in NSCLC.[2, 3] This is reflected by the clinical evidence base underpinning this submission: patients with NSCLC in the pivotal LIBRETTO-001 study were identified to have non-squamous histology in the overwhelming majority of cases. Furthermore, of the [redacted] patients recorded in the SACT dataset to have received selpercatinib, all of them had non-squamous tumour histology.[4] Consequently, the target population in this submission has been restricted to patients with tumours exhibiting non-squamous histology.
Intervention	Selpercatinib	Selpercatinib (160 mg twice daily [BID])	In line with the final NICE scope
Comparator(s)	For people with non-squamous cancer previously treated with platinum doublet chemotherapy or pemetrexed and carboplatin or cisplatin: • atezolizumab • docetaxel • docetaxel and nintedanib For people with programmed death-ligand 1 (PD-L1) positive non-squamous cancer previously treated with platinum doublet chemotherapy or pemetrexed and carboplatin or cisplatin:	For people with non-squamous NSCLC: • docetaxel monotherapy • docetaxel and nintedanib (TA347)[5]	This submission will focus on clinical evidence from patients with *RET* fusion-positive non-squamous NSCLC due to the rarity of *RET* fusion alterations in squamous disease, and in alignment with the population enrolled in the LIBRETTO-001 clinical trial. Therefore, comparators for the patient population with tumours exhibiting squamous histology are not considered to be relevant to the present scope, as per the approach taken in previous NICE appraisals of selpercatinib in NSCLC (TA760 and TA911) and

	• nivolumab • pembrolizumab For people with non-squamous cancer previously treated with pembrolizumab with pemetrexed and platinum chemotherapy or atezolizumab with bevacizumab, carboplatin and paclitaxel: • docetaxel • docetaxel and nintedanib For people with non-squamous cancer previously treated with pembrolizumab or atezolizumab monotherapy: • docetaxel • docetaxel and nintedanib • pemetrexed and carboplatin • pemetrexed and cisplatin • platinum doublet chemotherapy For people with squamous cancer previously treated with platinum doublet chemotherapy: • atezolizumab • docetaxel • nivolumab For people with PD-L1 positive squamous cancer previously treated with platinum doublet chemotherapy: • pembrolizumab		recent feedback from a UK clinical expert.[1, 2, 6] In further alignment with Committee preferences in the prior NICE appraisal of selpercatinib for previously treated *RET* fusion-positive advanced NSCLC (TA760), immunotherapies (atezolizumab, nivolumab and pembrolizumab) are not considered to be relevant comparators in the second-line setting in patients with *RET* fusion-positive non-squamous NSCLC, as patients would be expected to receive immunotherapies as a first-line treatment and so would not receive them again at second line.[2] The same Committee also concluded that pemetrexed with carboplatin and platinum doublet chemotherapy are not relevant comparators in patients with *RET* fusion-positive non-squamous NSCLC at second-line, as they are rarely used at this point in the treatment pathway.[2] The Committee's conclusion that immunotherapies, pemetrexed with carboplatin and platinum doublet chemotherapy are not relevant comparators to selpercatinib in this indication was supported by clinician feedback during the prior appraisal, and subsequently by more recent clinical expert feedback received during the preparation of this submission.[2, 6]

	For people with squamous cancer previously treated with pembrolizumab with carboplatin and paclitaxel: • docetaxel For people with squamous cancer previously treated with pembrolizumab or atezolizumab monotherapy: • platinum doublet chemotherapy		As such, in alignment with the Committee conclusions and clinical expert advice, Lilly maintain that docetaxel monotherapy and docetaxel with nintedanib are the only relevant comparators in this indication.[2]
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression free survival (PFS) • Response rate • Time to treatment discontinuation (TTD) • Adverse events (AEs) of treatment • Health-related quality of life (HRQoL)	Primary: • Objective response rate (ORR) Secondary: • Duration of response (DOR) • PFS • OS • TTD HRQoL: • European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30) Safety outcomes: • AEs	In line with the NICE final scope
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).	• 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	In line with the NICE final scope

	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 a 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 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 who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	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. • Proportional genetic testing costs will be included in the base case analysis of the submission but will be excluded as a scenario analysis as *RET* testing has become part of routine clinical practice due to the establishment of Genomic Hubs.[7, 8] Despite their inclusion in the base case, the costs of *RET* testing are anticipated to be absorbed by the NHS.[7]	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • tumour histology (squamous or non-squamous) and • level of PD-L1 expression	The following subgroup analysis are considered: • Subgroup analyses in *RET* fusion-positive advanced NSCLC patients with brain metastases	PD-L1 status was not collected in the pivotal LIBRETTO-001 trial, therefore subgroup analyses of patients based on PD-L1 expression were not able to be performed. In addition, the number of patients with *RET* fusion-positive, squamous NSCLC being treated in the second line was very low in the LIBRETTO-001 trial and as such, any subgroup analyses conducted would not be statistically robust.

			Moreover, the presentation of subgroup analyses would not be in line with the Committee's expectation in TA760 that the prescribing practice in the NHS for patients with advanced, *RET* fusion-positive NSCLC would be the same regardless of squamous or non-squamous tumour histology.[2] For these reasons, subgroup analyses by tumour histology were not performed. Subgroup analyses were conducted in patients with brain metastases. It has been found that approximately 50% of patients with *RET* fusion-positive NSCLC experience brain metastases, therefore subgroup analyses in this population were performed.[9]

Abbreviations: AE: adverse event; BID: twice daily; DOR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; 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; PD-L1: programmed death-ligand 1; PFS: progression free survival; PSS: Personal Social Services; QALY: quality-adjusted life year; RET: rearranged during transfection; SACT: systemic anti-cancer therapy; TA: technology appraisal; TTD: time to treatment discontinuation.

B.1.2 Description of the technology being evaluated

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

Table 2: Technology being appraised

UK approved name and brand name	Selpercatinib (Retsevmo®)
Mechanism of action	Selpercatinib is a first-in-class, orally available, highly selective small molecule inhibitor of fusion, mutant and wild-type products involving the proto-oncogene *RET* tyrosine kinase receptor.[10, 11] Administration of selpercatinib inhibits cell growth in tumour cells that exhibit increased RET activity.[10, 11]
Marketing authorisation/CE mark status	Relevant to the current submission, selpercatinib currently holds a conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for selpercatinib as monotherapy for the treatment of patients with advanced *RET* fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy, which was granted in March 2021 via the European Commission Decision Reliance Procedure (ECDRP).[10, 11] A licence extension was granted via the European Commission Decision Reliance Procedure (ECDRP) for use of selpercatinib in treatment-naïve advanced *RET* fusion-positive NSCLC in October 2022.[10, 11]
Indications and any restriction(s) as described in the SmPC	Selpercatinib as monotherapy is indicated for the treatment of adults with:[10, 11] • Advanced *RET* fusion-positive NSCLC not previously treated with a RET inhibitor • Advanced *RET* fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib Selpercatinib as monotherapy is also indicated for the treatment of adults and adolescents 12 years and older with advanced *RET*-mutant medullary thyroid cancer (MTC).[10, 11]
Method of administration and dosage	Oral selpercatinib 160 mg (2 x 80 mg capsules) twice daily (BID). Capsules of 40 mg are also available for patients who require dose adjustments.
Additional tests or investigations	An accurate and validated assay for *RET* is necessary for the selection of *RET* fusion-positive patients for treatment with selpercatinib. Testing of *RET* fusion status is routine in clinical practice in the UK, as genetic drivers of NSCLC, including *RET* fusion status, are tested for according to the national genomic test directory commissioned by the NHS.[7, 8]
List price and average cost of a course of treatment	The list price of a 112 hard capsule pack of 80 mg is £8,736.00 and the price of a 168 hard capsule pack of 40 mg selpercatinib is £6,552.00.[12] At list price, the cost of a 28-day cycle of selpercatinib is £8,736.00.
Patient access scheme (if applicable)	The company has incorporated the existing PAS discount already established in the NHS for selpercatinib. The PAS represents a simple discount of [redacted]% on the list price; at this discounted price, the 112 hard

	capsule pack of 80 mg selpercatinib costs £[redacted] and the 168 hard capsule pack of 40 mg selpercatinib costs £[redacted].

Abbreviations: BID: twice daily; CE: Conformité Européenne; MTC: medullary thyroid cancer; NHS: National Health Service; NSCLC: non-small cell lung cancer; PAS: patient access scheme; *RET*: rearranged during transfection; SmPC: summary of product characteristics; UK: United Kingdom.

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

Disease overview

- Lung cancer is the second most common cancer in England.[13] NSCLC accounts for between 80–85% of lung cancer cases, with an upper estimate of 2% of these cases exhibiting *RET* fusions.[3, 14] This equates to approximately 150 adults testing positive for *RET* fusion alterations in England and Wales in 2021.[3, 14, 15]
- The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. Owing to the ambiguity of common symptoms, a high proportion of patients are diagnosed at advanced stages of disease. Approximately 71% of patients were diagnosed with advanced lung cancer (stages III and IV) in England in 2020.[13]
- The five-year survival rate for patients diagnosed in the earlier stages of NSCLC is estimated to be 56.6%. However, this decreases markedly to 2.9% for advanced disease.[16]
- NSCLC represents a considerable humanistic burden, with patients diagnosed with NSCLC reporting lower HRQoL scores than the general population.[17, 18]

Clinical pathway and proposed positioning of selpercatinib

- Selpercatinib has previously been recommended for use via the CDF in patients with advanced, *RET* fusion-positive NSCLC in the second-line setting in the prior NICE appraisal, TA760 (the same patient population as the current submission).[2]
- Selpercatinib is also recommended by NICE (via the CDF) for untreated advanced, *RET* fusion-positive NSCLC (TA911).[1]
- Broadly, for patients with advanced, non-squamous NSCLC who have progressed from first line therapy, second-line therapeutic options are indicated depending on the first-line treatment received and the presence of identified genetic markers
- Selpercatinib would be positioned as a second-line treatment option for patients diagnosed with *RET* fusion-positive advanced, non-squamous NSCLC, should it be recommended for routine use.

Unmet need for a targeted treatment

- Recent establishment of testing for common oncogenic drivers of NSCLC (including *RET* fusion) at Genomic Hubs in England, has enabled physicians to prescribe targeted therapies, like selpercatinib, as first-line treatment.[1]
- However, delays in identifying patients' *RET* status in clinical practice, potentially resulting in part from insufficient biopsy yields, may result in clinicians needing to initiate standard-of-care (SOC) chemotherapy or immunotherapy before receiving results of genomic testing. A proportion of treatment-naïve patients may also begin SOC chemotherapy should the stage of their disease and resulting disease burden make any treatment delay clinically inappropriate.
- These 'bridging' therapies are essential for extending patient survival but mean that patients who start them and are subsequently diagnosed with *RET* fusion-positive NSCLC are pre-treated by the time eligibility for selpercatinib has been established. In this scenario, selpercatinib could be considered for use in the second-line setting.[14]
- Following its exit from CDF, a recommendation for selpercatinib in this second-line setting would mean it remains the only targeted treatment available to this patient population. Without selpercatinib, *RET* fusion-positive patients who received SOC chemotherapy first would not be able to access a targeted second-line RET inhibitor therapy, representing a significant unmet need. Moreover, this would place this patient population in stark contrast with *RET* fusion-positive patients who receive results of *RET* fusion testing in sufficient time to enable them to receive selpercatinib in the first-line setting.

B.1.3.1 Overview of the disease

Disease background

Lung cancer is the second most common cancer in England, accounting for approximately 13% of all newly diagnosed cancers, with 34,478 people being newly diagnosed with lung cancer in 2021.[13, 19] Lung cancer is also the leading cause of cancer-related death in England, with an age-standardised mortality rate for women and men of 43 and 58, respectively per 100,000 in 2020.[20] As such, lung cancer represents a key clinical and public health challenge.[21]

Lung cancer is termed "primary" when tumours first originate in lung tissue, usually in the cells lining the bronchi and other parts of the lung (e.g. bronchioles or alveoli). Lung cancer is divided into two main subtypes based upon the microscopic appearance of the tumour cells: small cell lung cancer and non-small cell lung cancer (NSCLC).[14] These subtypes progress and are treated in different ways, making their distinction clinically important. NSCLC accounts for the majority (80–85%) of lung cancer cases in the UK and can be sub-divided further into three histological groups: adenocarcinoma (the most common subtype in both men and women), large-cell undifferentiated carcinoma and squamous cell carcinoma.[22] Adenocarcinoma and large cell undifferentiated carcinoma comprise 40% and 5–10% of all lung cancer cases, respectively, and are frequently considered together under "non-squamous" histology.[23]

NSCLC can be further classified by genetic markers such as *EGFR* mutations, *ALK* translocation and *ROS-1* rearrangements.[24] *RET* fusion is one such marker, and positive patients account for approximately 1–2% of NSCLC cases. *RET* fusions are most commonly seen in adenocarcinoma, but have also been reported in mixed adenosquamous histology.[3] This is supported by a recent retrospective observational study published in 2021, which found that patients exhibiting metastatic NSCLC with *RET* alterations were more likely to have non-squamous histology than the general NSCLC population, as informed by the Flatiron-Foundation Medicine Clinico-Genomics Database (CGDB) in the United States.[25] Furthermore, of the [redacted] patients recorded in the SACT dataset to have received selpercatinib, all of them had NSCLC displaying non-squamous tumour histology.[4]

Rearranged during transfection (RET) tyrosine kinase

RET is a transmembrane receptor protein tyrosine kinase, which is present on the surface of several tissue types.[3] The RET protein is encoded by the *RET* gene, which under normal circumstances plays a role in cell growth, division and specialisation. Abnormal *RET* activation occurs through two mechanisms associated with malignancy: mutations and fusions, with the latter typically present in NSCLC. Fusions are generated by an inversion of the short and long arms of chromosome 10.[26] 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.[27]

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.[3] This leads to abnormal activation of the RET protein and, in turn, downstream signalling in the cell, including activation of MAPK, PI3K/AKT and JAK/STAT pathways.[3] Abnormal *RET* activity enhances cell survival, proliferation, transformation, migration and angiogenesis, making *RET* fusions an important oncogenic driver in NSCLC.[28] *RET* fusions tend to be mutually exclusive with other major lung cancer oncogenic drivers and therefore represent a unique molecular target.[29-31]

There are currently no studies reporting the prevalence of *RET* fusion-positive NSCLC patients in the UK, as studies reporting epidemiological data for *RET* fusion-positive NSCLC are limited in number and by geography. Consequently, epidemiological data for *RET* fusion-positive NSCLC specifically in the UK are currently restricted to estimates using available statistics. Using data from the Office of National Statistics, the National Lung Cancer Audit database, Cancer Research UK, Royal College of Physicians, and an estimate of 1% from Kohono *et al.* 2012, approximately 150 adults being diagnosed with advanced NSCLC who are *RET* fusion-positive in England and Wales each year.[3, 31-33]

Disease progression and prognosis

The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. NSCLC can be categorised into four principal stages, with Stages IIIB–C (the cancer is 5–7 cm in size and has spread to lymph nodes, different lobes of the lungs and/or other organs in the chest as a single or greater than one tumour) and IV (the cancer has spread to both lungs and/or other parts of the body) grouped under the classification "advanced".[34, 35] The five-year survival rate in England for those diagnosed in earlier stages of NSCLC disease is estimated to be 40–65%, which decreases to 5–15% for those diagnosed at advanced stages.[36] 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.[24]

The majority of new lung cancer cases in England are diagnosed at Stage III or IV (71% in 2020).[13] Diagnosis in an advanced stage of disease is commonly due to the ambiguity of symptoms, such as fatigue, loss of appetite, chest pain, weight loss and respiratory problems and the rapid growth of untreated tumours.[13] Untreated NSCLC is characterised by rapid growth and progression to advanced disease, with a small untreated tumour lesion typically progressing to advanced stages of disease in less than one year, compounding the effects of delayed diagnosis.[37, 38] Consequently, prognosis for lung cancer is poor, with only 45% of patients surviving more than one year following diagnosis in England in 2021.[39]

There are limited published data on the survival of patients with advanced *RET* fusion-positive NSCLC. The IMMUNOTARGET registry examined patients diagnosed with advanced NSCLC with a range of different molecular subtypes, including *RET* fusion, treated with first- or second-line immunotherapy (N=551 from 10 countries).[40] Median PFS ranged between 2.1–3.4 months, whilst median OS ranged between 10.0–21.3 months.[40] 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.[40]

While a positive *RET* fusion status may seem to be associated with improved prognosis compared to other forms of NSCLC, patients with *RET* fusion-positive NSCLC typically tend to be younger, have a non-smoking status and have a better tumour performance score than the general NSCLC population which may confound this association. In fact, based on current evidence, there is no clear statistically significant evidence that *RET* alterations have a prognostic influence, as demonstrated by an analysis reported by Hess *et al.* (2021) which studied tumour response outcomes in 5,807 NSCLC patients (*RET* fusion-positive: 46; *RET* fusion-negative: 5,761) in the United States using data from the Flatiron CGDB.[25] This study reported that there was a significant difference in OS between patients with *RET* fusions and those without (hazard ratio [HR]: 1.91; 95% CI: 1.22–3.0; p=0.005), but there was no statistically significant difference in PFS (p=0.06).[25] However, after adjusting for baseline covariates, there was no statistically significant difference identified for either PFS (HR: 1.24; 95% CI: 0.86–1.78;

p=0.25) or OS (HR: 1.52; 95% CI: 0.95–2.43; p=0.08) in patients treated with standard therapy prior to the availability of selective RET inhibitors.[25] While acknowledging the limitations of this study, such as the small sample size of the *RET* fusion-positive population and potential unmeasured confounding, the lack of statistically significant difference in adjusted survival outcomes by *RET* status evidences that *RET* fusion may not be inherently prognostic. This is supported by recent feedback from a UK clinical expert, who confirmed that despite the availability of some real-world data, it currently remains unclear as to whether *RET* fusion status has an effect on prognosis of patients with NSCLC.[6]

Burden of disease

NSCLC represents a humanistic and economic burden on society. Disease symptoms caused by NSCLC, and the various therapies used to cure or manage them, impact the emotional and physical functioning of patients.[41, 42] However, there is a paucity of data on the HRQoL impact of *RET* fusion-positive NSCLC specifically. As such, these data presented relate to NSCLC, regardless of genomic alteration and/or biomarker expression, although they are anticipated to reflect the experience of patients with *RET* fusion-positive NSCLC.

The symptomatic and HRQoL burden of NSCLC are closely related. The earliest stage of NSCLC is often asymptomatic, but patients experience greater symptom burden and subsequently lower quality of life (QoL) as their disease progresses.[43, 44] Common physical symptoms of NSCLC include fatigue (98%), loss of appetite (98%), respiratory problems (94%), cough (93%), pain (90%) and blood in sputum (70%).[41, 44] At advanced stages, the cancer may spread to the lymph nodes, brain, liver, adrenal glands and/or the bones, bringing additional symptoms associated with the secondary tumour's location.[45]

Brain metastases occur frequently in patients with *RET* rearrangements, with an estimated lifetime prevalence of brain metastases of 46% in patients with stage IV *RET*-rearranged lung cancer.[46] The occurrence of brain metastases result in additional symptoms (e.g. confusion, headaches and changes of behaviour), complications to treatment and poorer patient prognosis and QoL.[46] 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).[47]

In addition to the physical symptoms of NSCLC, the mental health of patients is also impacted. Receiving a lung cancer diagnosis, treatment and conversations surrounding prognosis negatively affect the mental wellbeing of patients, with depression reportedly affecting between 23–40% of patients, and anxiety affecting an estimated 16–23% of patients.[41] As a result of this combined impact on their physical and mental wellbeing, patients are increasingly unable to complete activities perceived as "normal" in their family and social roles.[41]

Consequently, the HRQoL in NSCLC patients is lower than in the general population.[18] A 2018 systematic review highlighted that among patients receiving second-line treatment for advanced NSCLC, mean EQ-5D scores ranged between 0.53–0.82, with the highest values being associated with tyrosine kinase inhibitor treatment.[18] A similar range was seen among patients being treated for advanced NSCLC, where the treatment line was unspecified (0.53–0.77).[18] 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).[18] All scores were lower than the index EQ-5D score, calculated for the general population in England (0.85).[17]

Furthermore, 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.[48] 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.[49] 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.[50] Due to the impact of NSCLC on patients' mental and physical health, work life is also negatively affected, leading to indirect costs to society through absenteeism, lost productivity and early retirement.[51]

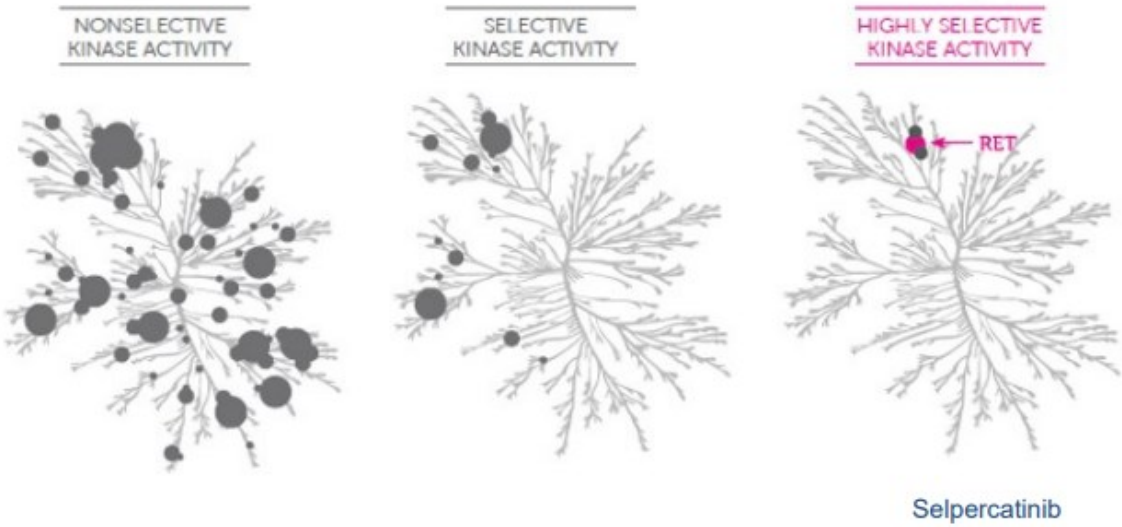
Selpercatinib

Selpercatinib is a highly selective inhibitor of fusion, mutant and wild-type products involving the proto-oncogene receptor tyrosine kinase *RET*.[52] The drug acts as an inhibitor of the RET kinase enzyme and prevents tumour cell growth.[52] Selpercatinib has shown promising activity in advanced *RET* fusion-positive solid tumours and is approximately 250-fold more selective for RET relative to other kinases (Figure 1).[53] 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.[3]

The safety and efficacy of selpercatinib has been assessed during an ongoing open-label single-arm Phase I/II clinical trial (LIBRETTO-001; NCT03157128) in patients with advanced solid tumours exhibiting *RET* rearrangements.[54] 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, Phase II dose-expansion was initiated, with treatment-naïve and pre-treated advanced NSCLC patients receiving 160 mg BID, and the anti-tumour activity of selpercatinib was analysed.[51, 54] Selpercatinib is also being explored in LIBRETTO-431 (NCT04194944), a randomised, open-label, Phase III trial comparing selpercatinib to platinum-based and pemetrexed therapy, with or without pembrolizumab, as first-line treatment for advanced or metastatic *RET* fusion-positive NSCLC.[55] An interim efficacy analysis of LIBRETTO-431 based on PFS has now been published.[56]

A conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for selpercatinib as monotherapy for the treatment of patients with advanced *RET* fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy was granted in March 2021.[10, 11] Use of selpercatinib for patients with previously-treated advanced *RET* fusion-positive NSCLC is also recommended under the CDF by NICE in TA760, making it the first RET kinase inhibitor to be available in England and Wales for these patients.[2] A licence extension was granted for the use of selpercatinib in treatment-naïve advanced *RET* fusion-positive NSCLC in October 2022,[10, 11] and selpercatinib has since been recommended by NICE via the CDF for advanced *RET* fusion-positive NSCLC in the first-line setting (TA911).[1]

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



Footnotes: The diagram depicts the activity of different kinases. It highlights that multi-kinase drugs influence a wide variety of kinases, frequently producing adverse side effects. The specificity of selpercatinib to the RET kinase is anticipated to provide enhanced efficacy and tolerability.
Abbreviations: RET: rearranged during transfection.
Source: Drilon *et al.* (2018).[53]

B.1.3.2 Clinical pathway of care

The treatment of NSCLC in the UK has been assessed by NICE through both published guidelines (NG122) and previous technology appraisals (TAs).[24] Given that there are no other RET kinase inhibitors recommended by NICE in the pre-treated setting at present, the treatment pathway for *RET* fusion-positive NSCLC described below has been informed by current guidance available from NICE for the treatment of NSCLC in the second-line setting more widely.[24]

NICE-recommended treatment pathway for patients with advanced, non-squamous, *RET* fusion-positive NSCLC in the second-line setting

Treatment of NSCLC is dependent on the disease stage at diagnosis, cancer histology (squamous and non-squamous) and the presence/absence of genomic drivers and biomarkers (e.g. PD-L1 status; an immune checkpoint protein expressed on the surface of cancer cells).[14, 24] In England, next generation sequencing (NGS) is the standard diagnostic practice to identify key oncogenic drivers in NSCLC (*EGFR*, *ROS1*, *ALK, BRAF V600, KRAS G12C, METex14* skipping alteration*, NTRK* fusion and *RET* fusion).[7, 8, 24] NGS is performed in Genomic Hubs, and allows a range of genetic mutations, rearrangements and fusions (including *RET* fusions) to be identified.[7, 8] This expedites the diagnostic process and grants clinicians the opportunity to prescribe targeted therapies, like selpercatinib, in the advanced disease setting.

For patients diagnosed with early-stage NSCLC (Stage I–II and usually IIIA), treatments with curative intent are indicated. These include surgery, radiotherapy, chemotherapy and multimodality treatment.[24] However, for patients who present with, or progress to, advanced (Stage IIIB/C or IV) NSCLC, treatments with curative intent are not suitable. Instead, NICE recommends systemic anti-cancer therapies to delay progression and extend survival for as long as possible, with treatment choice informed by the histology, biomarkers and genetic markers of the patient's tumour.[24]

It is standard clinical practice for patients with identified genetic markers to receive treatments targeted at that genetic marker, rather than by their other biomarker status (i.e. PD-L1 <50% or ≥50%). However, should selpercatinib cease to be available to treat patients with advanced *RET* fusion-positive NSCLC in the second line after its exit from the CDF, this patient population would be treated with the same set of therapies as patients not exhibiting genetic markers. Patients with oncogene-driven NSCLC, such as *RET* fusion-positive, *EGFR* mutations, *ALK* translocations or *ROS-1* rearrangements, typically have just one genetic marker, as these mutations are typically mutually exclusive.[51, 57, 58] Therefore, patients with *RET* fusion-positive, advanced NSCLC would not benefit from other oncogene-targeted therapies.

As described previously, patients with *RET* fusion-positive NSCLC predominantly have tumours with non-squamous histology.[3] NICE recommends a number of therapy options in the second line for patients with advanced, *RET*-fusion positive NSCLC who have previously received one line of therapy (Figure 2). Since the entry of selpercatinib into the CDF (TA760),[2] there has been an increase in therapy options recommended by NICE for patients with NSCLC with a targetable gene mutation or fusion protein in the second-line setting.

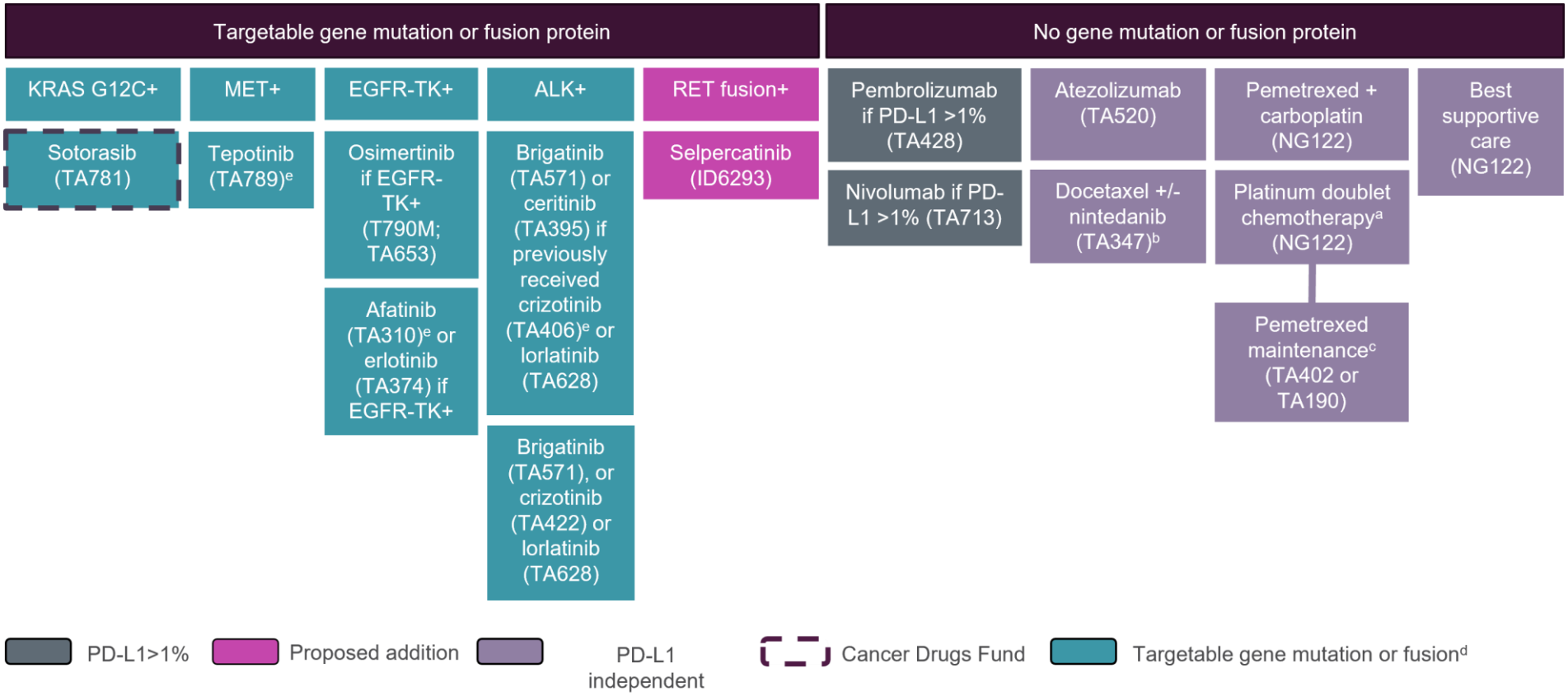
NICE recommends the following second-line treatment options in non-squamous NSCLC according to whether or not a patient has cancer with a targetable gene mutation or fusion protein:

- *EGFR-TK* mutation: afatinib (TA310),[59] erlotinib (TA374)[60] or osimertinib if their tumours carry the T790M mutation (TA653)[61]
- *ALK* translocation: lorlatinib (TA628)[62], brigatinib (TA571),[63] crizotinib (TA422)[64]
- *ALK* translocation (patient previously treated with crizotinib (TA406)[65] or lorlatinib (TA628)[62] in the first-line setting): brigatinib (TA571),[63] ceritinib (TA395)[66]
- *MET* mutation: tepotinib (TA789)[67]
- *KRAS* G12C: sotorasib is available via the CDF (TA781)[68]

Patients with non-squamous NSCLC without a targetable gene mutation or fusion protein receive treatments based on their other biomarker status (i.e. PD-L1). For patients with a PD-L1 tumour proportion score of >1%, pembrolizumab monotherapy (TA428)[69] and nivolumab (TA713)[70] are recommended. [2, 6]

In the absence of a targetable gene mutation or fusion protein and regardless of other relevant biomarkers in this patient population, NICE has previously recommended treatment with atezolizumab (TA520)[71], docetaxel with nintedanib (TA347; docetaxel monotherapy is also indicated – NG122)[5, 24], pemetrexed in combination with carboplatin (NG122),[24] platinum doublet chemotherapy (NG122)[24] with or without subsequent pemetrexed maintenance therapy (TA402 and TA190),[72, 73] and best supportive care (NG122).[24] However, clinician feedback during TA760 and more recent clinical expert feedback received during the preparation of this submission indicated that immunotherapy and platinum-based chemotherapies are used as first-line treatments, but they would not be given in the second line if the presence of *RET* alterations.[2, 6]

Figure 2: NICE-recommended treatment pathway for advanced, non-squamous NSCLC in the second-line setting



Footnotes: [a]Platinum doublet chemotherapy may include platinum-based chemotherapy (carboplatin/cisplatin) + paclitaxel, docetaxel gemcitabine or vinorelbine; or cisplatin + pemetrexed.
[b]TA347 (nintedanib + docetaxel) recommends 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.
[e]The NICE recommendations for afatinib (TA310), crizotinib (TA406) and tepotinib (TA789) encompass the first- and second-line settings.
Abbreviations: ALK: anaplastic lymphoma kinase; EGFRex20: epidermal growth factor receptor gene exon 20 insertion; EGFR-TK: epidermal growth factor tyrosine kinase; KRAS: Kirsten rat sarcoma virus; MET: mesenchymal epithelial transcription factor; NICE: National Institute for Health and Care Excellence; NG: NICE guideline; PD-L1: programmed death ligand 1; RET: rearranged during transfection; TA: technology appraisal.

Positioning of selpercatinib in the treatment pathway and unmet need

In this submission, selpercatinib is positioned as a second-line treatment option for patients diagnosed with advanced non-squamous *RET* fusion-positive NSCLC. *RET*-specific treatment offers improved clinical effectiveness and tolerability compared with other available treatments in *RET* fusion-positive NSCLC. The specificity of targeted treatments, like selpercatinib, are anticipated to deliver substantially superior efficacy outcomes compared to non-targeted treatments such as immunotherapies and chemotherapy. Indeed, there is evidence to suggest that *RET*-rearranged lung cancers are characterised by low levels of PD-L1 expression, suggesting that these tumours are "biologically cold" and less likely to be highly responsive to immunotherapy relative to other cancers.[74] In addition, adverse events from non-targeted immunotherapies can affect one or several different organ systems, with an incidence of Grade 3 and higher toxicities of 7–13%.[75]

Via the CDF (TA760),[2] selpercatinib was the first RET-targeted treatment available for pre-treated patients and would continue to fulfil a significant unmet need in this population, if recommended for use via routine commissioning.

Selpercatinib is also recommended in the first-line setting for *RET* fusion-positive advanced NSCLC (TA911).[1] Consequently, in theory, all eligible patients could currently receive selpercatinib in the first-line setting. Although molecular testing at Genomic Hubs should allow most patients to receive selpercatinib as a first-line treatment, this may not be the case for some patients, such as when delays in testing occur due to initial biopsy yield being insufficient for testing, or where there is an urgent clinical need to treat the patient prior to the establishment of their *RET* status.[14] Consequently, a proportion of eligible, untreated patients begin SOC chemotherapy prior to receiving the results of *RET* fusion testing in clinical practice, since the advanced stage of their disease and resulting disease burden makes waiting for these results prior to treatment commencement clinically inappropriate. These bridging therapies are essential for extending patient survival but mean that patients who start SOC chemotherapy and are then subsequently diagnosed with *RET* fusion-positive NSCLC would be pre-treated by the time eligibility for selpercatinib has been established. In addition, in the period between selpercatinib becoming available in the first- and second-line settings (i.e., between publication of TA760 and TA911 in January 2022 and July 2023, respectively) some patients may have initiated first-line therapies anticipating the availability of selpercatinib at second-line.[1]

If recommended via routine commissioning after exit from the CDF, selpercatinib would remain the only targeted treatment available for previously treated patients with advanced, *RET* fusion-positive NSCLC. However, if selpercatinib were no longer available in the second-line setting, these patients would instead receive the same second-line treatment options as patients with no recognised oncogenic drivers. This would constitute a significant unmet need in this patient population who would be in stark contrast with *RET* fusion-positive patients who receive results of *RET* fusion testing in sufficient time to enable them to receive selpercatinib in the first-line setting.

In clinical practice, selpercatinib would be expected to continue being prescribed in place of second line, non-targeted treatments previously received by patients with a positive *RET* status in England and Wales.

Accordingly, as a RET receptor kinase inhibitor with high specificity, selpercatinib is anticipated to continue to fulfil a significant unmet need in England and Wales for an efficacious, targeted

therapy with a tolerable safety profile in pre-treated patients with advanced *RET* fusion-positive NSCLC.

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 than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

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

Efficacy outcomes

- The efficacy of selpercatinib in previously treated *RET* fusion-positive NSCLC has been demonstrated in LIBRETTO-001, a first in-human, Phase I/II, single arm, open-label trial.
- Data presented in this submission are from the Integrated Analysis Set (IAS, N=247) of the LIBRETTO-001 trial at the 13th January 2023 data cut-off. The IAS represents all previously treated NSCLC patients enrolled on the LIBRETTO-001 trial before or on the date of data cut-off. Compared with the previous data cut-off presented in the prior submission of selpercatinib in this indication (TA760), these data provide:[2, 76]
    - Longer follow up: An additional 30.29 months and 27.6 months of follow-up for overall survival (OS) and progression-free survival (PFS) data, respectively, are available.[77, 78]
    - Larger population of enrolled patients: By the 13th January 2023 data cut-off, there were [redacted] more patients in the IAS population compared to the IAS population previously presented.[77, 78]
- As a result, the survival data presented in this submission are associated with considerably reduced uncertainty compared to data presented in TA760.[2]
- The primary endpoint of LIBRETTO-001 was overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of either a confirmed complete response (CR) or partial response (PR) based on RECIST v1.1 and Independent Review Committee (IRC) assessment. The ORR in previously treated *RET* fusion-positive NSCLC patients was 61.5% (152/247; 95% CI: 55.2–67.6).
- Key secondary outcomes assessed during LIBRETTO-001 included duration of response (DOR), PFS and OS by IRC assessment. In previously treated *RET* fusion-positive NSCLC patients in the IAS:[79]
    - The median DOR was 31.64 months (95% CI: 20.4–42.3), with progressed disease (PD) observed in [redacted] patients, and a median follow-up of 39.52 months.[76]
    - The median PFS by IRC assessment was 26.15 months (95% CI: 19.3–35.7). Death or disease progression was reported in [redacted]247[redacted] patients at a median follow-up of 41.2 months.[76]
    - The median OS was 47.57 months (95% CI: 35.9–NE) with a median follow-up of 44.55 months.[76]

Summary of indirect treatment comparison

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

Indirect treatment comparison results

- Treatment with selpercatinib resulted in higher odds of ORR when compared to nintedanib plus docetaxel chemotherapy (OR [95% CrI]: [redacted] [redacted], [redacted]]) and docetaxel monotherapy (OR [95% CrI]: [redacted] [redacted], [redacted]), respectively.
- In addition, treatment with selpercatinib and had a lower hazard of progression or death (PFS) compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted] [redacted], [redacted]]) and docetaxel monotherapy (HR [95% CrI]: [redacted] [redacted], [redacted]]), respectively.
- Similarly to PFS, treatment with selpercatinib and demonstrated a lower risk of death (OS) when compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted] [redacted], [redacted]]) and docetaxel monotherapy (HR [95% CrI]: [redacted] [redacted], [redacted]]), respectively.

Summary of adverse events

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (OSAS) (regardless of tumour type or treatment history) and patients in the IAS trial population.
  - Grade 3 or 4 TEAEs were reported in [redacted] patients in the OSAS population and in [redacted] patients in the IAS population. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication.[80]
- Overall, selpercatinib was shown to be well tolerated across patient populations and, considering the clinical efficacy demonstrated in patients with *RET* fusion-positive NSCLC, selpercatinib has demonstrated a positive risk:benefit ratio in this population.

Interpretation and conclusions

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

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for advanced *RET* fusion-positive NSCLC who require systemic therapy, including adults who have been previously treated. The original SLR was conducted in September 2019, and subsequently underwent three updates in October 2020, July 2021 and January 2024.

Following de-duplication of results for NSCLC studies identified in the SLR searches, a total of 8,533 publications were screened at the title and abstract stage, of which 3,660 publications were reviewed at the full-text stage. After exclusion of publications not meeting the eligibility criteria, 428 publications (reporting on 155 unique studies; 14 of which were studies reporting on *RET*-altered cancers) were included in the SLR for NSCLC. Full details of the SLR search strategy, study selection process and results are presented in Appendix D.2. A risk of bias assessment was conducted on all included studies to standards recommended by NICE, the results for which are presented in Section B.2.5 and Appendix D.2.5.[81]

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical effectiveness of selpercatinib in *RET* fusion-positive NSCLC was assessed in LIBRETTO-001, a multi-centre, open-label, single-arm, Phase I/II trial. Phase I was designed to understand the pharmacokinetics (PK), safety and maximum tolerated dose (MTD) of selpercatinib, whilst Phase II was designed to perform a preliminary assessment of the efficacy and safety of selpercatinib in patients with *RET*-altered solid tumours. The study commenced in May 2017 and is the first in-human Phase I/II study for selpercatinib. An overview of LIBRETTO-001 is included in Table 3.

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

Table 3: Clinical effectiveness evidence

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[82]
Study design	LIBRETTO-001 is a multicentre, open-label, single-arm, Phase I/II study. The trial is demarcated into two parts: Phase I (dose escalation) and Phase II (dose expansion).
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g. NSCLC, thyroid, pancreas or colorectal), *RET*-mutant medullary thyroid cancer (MTC) and other tumours with RET activation, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and have an Eastern Cooperative Oncology Group (ECOG) score ≤2 or a Lansky Performance Score (LPS) ≥40%. ***RET* fusion-positive NSCLC patients who have received at least one prior line of anti-cancer therapy are the focus of this submission.** As of 13th January 2023, N=837 patients had been enrolled onto the trial, of which N=247 were treatment-exposed *RET* fusion-positive NSCLC patients and make up the integrated analysis set (IAS).
Intervention(s)	Selpercatinib, once or twice daily, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study.
Comparator(s)	N/A – LIBRETTO-001 is a single am trial
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use in the model	LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with previously treated *RET* fusion-positive NSCLC.
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • PFS • OS HRQoL: • EORTC QLQ-C30 Safety outcomes: AEs

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[82]
All other reported outcomes	DOR

Abbreviations: AEs: adverse events; BID: twice daily; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; HRQoL: health-related quality of life; IAS: integrated analysis set; LPS: Lansky Performance Score; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression free survival; *RET:* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76]

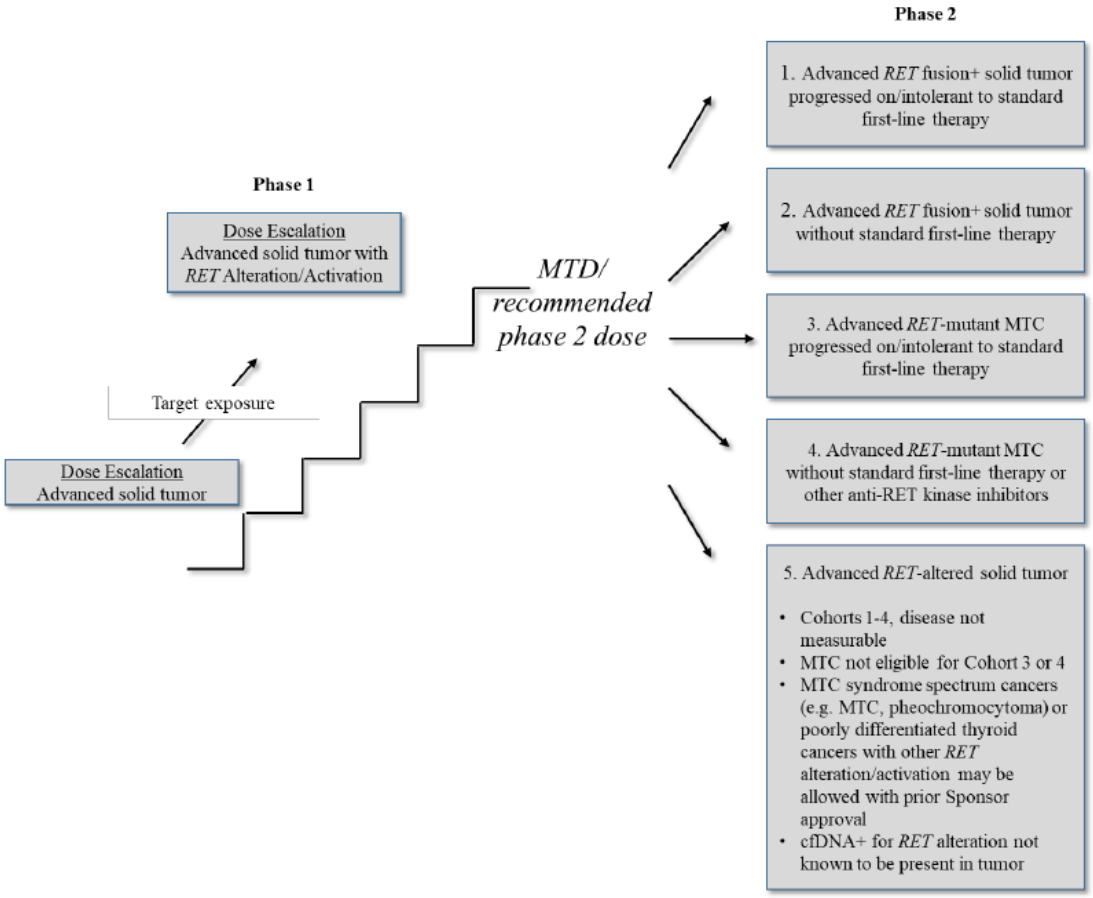
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

LIBRETTO-001 is a multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including *RET* fusion-positive NSCLC tumours.[83] The patient population includes patients ≥12 years of age with a locally advanced or metastatic solid tumour, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for, or would be unlikely to tolerate or derive significant clinical benefit from, standard therapy or declined standard therapy. Patients were screened for eligibility based on the criteria presented in Table 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 was assessed. The study is currently in Phase II.[84] A schematic of the trial is presented in Figure 3. The LIBRETTO-001 trial is currently ongoing and the most recent data cut-off from the study, presented in this submission, was performed on 13th January 2023. [redacted].

Figure 3: Study schematic of the LIBRETTO-001 trial



Abbreviations: MTC: medullary thyroid cancer; MTD: maximum tolerated dose; cfDNA: cell free DNA; *RET*: rearranged during transfection.
Source: Drilon et al. 2020b.[83]

The primary objective of Phase I was to determine the MTD and the recommended Phase II dose (RP2D). Based on results from Phase I escalation phase, the safety review committee (SRC) selected an RP2D of 160 mg.[85]

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 treatment-naïve *RET* fusion-positive NSCLC.
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib.
Cohort 4	*RET*-mutant MTC without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity.
Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3

	or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample.
Cohort 6	Patients otherwise eligible for Cohort 1–5 but who discontinued another selective *RET* inhibitor(s) due to intolerance are eligible with prior Sponsor approval.

Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.
Source: Drilon et al. 2020b.[83]

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.[85] The primary endpoint for the Phase II portion of the trial was ORR using RECIST v1.1. Secondary endpoints included DOR, PFS and OS, whilst the safety, tolerability and PK properties of selpercatinib were also considered.

In line with the decision problem for this submission, only results for the clinical effectiveness of selpercatinib in previously-treated patients with *RET* fusion-positive NSCLC (Cohort 1) 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 below.

Table 5: Summary of LIBRETTO-001 trial methodology

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

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

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

	• Fusion partner:
	  • KIF5B
	  • CCDC6
	  • NCOA4
	  • KIAA1468
	  • ARHGAP12
	  • CCDC88C
	  • CLIP1
	  • PRKAR1A
	  • RBPM and DOCK 1
	  • TRIM24
	  • Other
	  • Unknown
	• Molecular assay:
	  • NGS on blood or plasma
	  • NGS on tumour
	  • PCR
	  • Other

Duration of study and follow-up	The first patient was treated on 9th May 2017. Three data cut-offs have been recorded throughout the trial period: • 16th December 2019, the median follow-up was [redacted] months for OS and [redacted] months for PFS for IAS.[2] • 30th March 2020, the median follow up was [redacted] months for OS and [redacted] months for PFS for IAS.[77, 78] • 15th June 2021, the median follow-up was 26.4 months for OS and 24.7 months for PFS for IAS.[86] • 13th January 2023, the median follow-up was 44.6 months for OS and 41.2 months for PFS for IAS.[80] This is the latest data-cut and is presented throughout this submission. 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; IAS: integrated analysis set; 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; SFU: safety follow-up.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off);[76] Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off);[86] TA760;[2] Drilon *et al.* 2020a.[54] Drilon et al. 2022.[80]

B.2.3.3 Baseline characteristics

A summary of patient demographics and other baseline characteristics for the 247 patients in the IAS population with *RET* fusion-positive NSCLC enrolled in LIBRETTO-001 is provided below.[80]

The median age of patients was 61.0 (range: 23–81) years, with a greater proportion of female participants (56.7%; Table 6) than male participants. A high proportion of patients were white (43.7%) or identified as Asian (47.8%), and most participants reported never smoking (66.8%).[80] The younger age, as well as the higher proportion of females, Asian patients and non-smokers is consistent with the patient profile of *RET* fusion-positive NSCLC reported in the literature, and mirrors the real-world patient profile in England.[3, 40]

The median time from diagnosis was [redacted] months ([redacted]) (Table 7). Most patients ([redacted]%) had metastatic disease at enrolment, with 31.2% of patients exhibiting CNS metastases at baseline. Of the patients with advanced NSCLC in the IAS population, most patients were diagnosed with Stage IV or greater disease ([redacted]%), which closely reflects the proportion of patients with Stage III or IV lung cancer being diagnosed with Stage IV disease in clinical practice in England: in 2021, 70.7% of patients diagnosed with Stage III or IV lung cancer in England were diagnosed at Stage IV.[87, 88] NGS on tumour samples ([redacted]%) was the most common method of determining *RET* fusion status, which mirrors clinical practice in England following the establishment of Genomic Hubs (Table 7).[8]

In line with the population described in the decision problem, all patients in the IAS population had received prior systemic therapy, with the majority also having received radiotherapy ([redacted]%; Table 8).

Table 6: Baseline demographic characteristics for treatment-exposed *RET* fusion-positive NSCLC patients (IAS)

Characteristics	IAS (treatment-exposed), N=247
Age, years	
Median (range)	61.0 (23–81)
Age group, n (%)	
18–44 years	[redacted]
45–64 years	[redacted]
65–74 years	[redacted]
75 –84 years	[redacted]
≥85 years	[redacted]
Sex, n (%)	
Male	107 (43.3)
Female	140 (56.7)
Race, n (%)	
White	108 (43.7)
Black	12 (4.9)
Asian	118 (47.8)
Other/Missing	9 (3.6)

Ethnicity, n (%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Missing	[redacted]
Body weight, kg	
Median (range)	[redacted]
Baseline ECOG, n (%)	
0	90 (36.4)
1	150 (60.7)
2	7 (2.8)
Smoking history, n (%)	
Never smoked	165 (66.8)
Former smoker	78 (31.6)
Current smoker	4 (1.6)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; IAS: integrated analysis set.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Drilon *et al.* 2022.[80] Table JZJA.8.12

Table 7: Baseline disease characteristics for treatment-exposed *RET* fusion-positive NSCLC patients (IAS)

Characteristics	IAS (treatment-exposed), N=247
Stage at diagnosis, n (%)	
I, IA, IB	[redacted]
II, IIA, IIB	[redacted]
IIIA, IIIB	[redacted]
IIIC	[redacted]
IV	[redacted]
IVA	[redacted]
IVB	[redacted]
IVC	[redacted]
Missing	[redacted]
Primary diagnosis, n (%)	
NSCLC	[redacted]
Adenocarcinoma	221 (89.5)
Large cell neuroendocrine carcinoma	3 (1.2)
Squamous cell carcinoma	1 (0.4)
Other	[redacted]
Unknown	22 (8.9)
Time from diagnosis, months	
Median (range)	[redacted]
History of metastatic disease, n (%)	
Yes	[redacted]
No	[redacted]

Time from diagnosis of metastatic disease, months	
Median	[redacted]
Range	[redacted]
At least 1 measurable lesion by investigator, n (%)	
Yes	[redacted]
No	[redacted]
Sum of diameters at baseline by investigator, mm	
Median (range)	[redacted]
CNS metastases at baseline by investigator, n (%)	
Yes	77 (31.2)
No	[redacted]
***RET* fusion partner, n (%)**	
KIF5B	153 (61.9)
CCDC6	53 (21.5)
NCOA4	5 (2.0)
Other	15 (6.1)
Unknown	[redacted]
Molecular assay type, n (%)	
NGS on tumour	[redacted]
PCR on tumour	[redacted]
NGS on plasma/blood	[redacted]
FISH on tumour	[redacted]
Other	[redacted]

Abbreviations: CNS: central nervous system; FISH: fluorescent in situ hybridisation; IAS: integrated analysis set; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; PCR: polymerase chain reaction; RET: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Drilon *et al.* 2022.[80] Table JZJA.8.16. and Table JZJA.8.17.

Table 8: Prior cancer-related treatments for *RET* fusion-positive NSCLC (IAS)

Characteristics	IAS (treatment-exposed), N=247
Prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Number of prior systemic regimens, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
≥3	107 (43.3)
Median (range)	2.0[redacted]
Prior radiotherapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior cancer related surgery, n (%)	

Yes	[redacted]
No	[redacted]

Abbreviations: IAS: Integrated Analysis Set.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Table JZJA.4.16 and JZJA.8.24

Participants flow

The patient disposition of the IAS is presented in Table 9. [redacted] ([redacted]%) patients from the IAS were still on treatment as of the 13th January 2023 data cut-off.[76] The most common reason for treatment discontinuation was disease progression ([redacted]247[redacted]).[89]

Table 9: Patient disposition of *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (13th January 2023 data cut-off)

Characteristics	IAS (treatment-exposed), N=247
Treated, n (%)	[redacted]
Treatment ongoing, n (%)	[redacted]
Treatment discontinued, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]
Other	[redacted]
Treatment continued post-progression, n (%)	[redacted]
Study status:	
Continuing study, n (%)	[redacted]
Discontinued study, n (%)	[redacted]
Reason for study discontinuation	
Withdrawal of consent	[redacted]
Death	[redacted]

Abbreviations: IAS: Integrated Analysis Set.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Drilon *et al.* 2022.[80] Table JZJA.4.1 and Table JZJA.8.7.

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

Analysis sets

There were 5 analysis sets in LIBRETTO-001 for patients with NSCLC (Figure 4 and Table 10). In line with the decision problem, only clinical effectiveness data from previously treated patients are considered in this submission. These patients comprised Integrated Analysis Set (IAS). The IAS (N=247) consists of all patients with *RET* fusion-positive NSCLC who enrolled on the LIBRETTO-001 trial either on or before the data cut-off.

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

Abbreviations: BID: twice daily; CNS: central nervous system; CSR: clinical study report; IRC: Independent Review Committee; MTC: medullary thyroid cancer; MTC:Cab/Van: patients previously treated with cabozantinib and/or vandetanib; MTC:Cab/VanNaive: patients not previously treated with cabozantinib and/or vandetanib; N: number of patients in the population; NMD: non-measurable disease; NSCLC: non-small cell lung cancer; NSCLC:PlatChemo: patients previously treated with platinum-based chemotherapy; NSCLC:TrtNaive: treatment-naive patients; QD: once daily; RAI: radioactive iodine; RET: rearranged during transfection; TC: thyroid cancer; TC:TrtSys: patients previously treated with systemic therapy other than RAI; TC:TrtSysNaive: patients not previously treated with systemic therapy other than RAI
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76]

Table 10: LIBRETTO-001 analysis set definitions

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
Integrated Analysis Set (second line)	All *RET* fusion-positive NSCLC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1–4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.		247
Primary Analysis Set (second line)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase I and Phase II who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive RET fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included 2. Measurable disease by RECIST v1.1 by IA[a] 3. Received 1 or more lines of prior platinum-based chemotherapy 4. Received 1 or more doses of selpercatinib		105
Supplemental Analysis Sets	• All other *RET* fusion-positive NSCLC patients (e.g. not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date • SAS1 and SAS2: met PAS criteria 1, 2 and 4 • SAS3: met PAS criteria 1 and 4 • SAS assignment was non-overlapping; thus SAS1–3 are mutually exclusive with each other.	SAS1 (treatment-naïve; population of interest to this submission): • No prior systemic therapy	69
		SAS2 (prior other systemic therapy): • Received prior systemic therapy other than platinum-based chemotherapy	[redacted]
		SAS3 (non-measurable disease): • No measurable disease[b]	[redacted]
Safety analysis			
Overall Safety Analysis Set	Patients treated with selpercatinib as of a data cut-off of 13th January 2023.	**NSCLC Safety Analysis Set:** *RET* fusion-positive NSCLC	362
		RET-mutant MTC	[redacted]
		RET fusion-positive thyroid cancers	[redacted]
		RET fusion-positive other cancers	[redacted]
		Other cancers	[redacted]
		Total	837

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; RECIST v1.1: Response Evaluation Criteria in Solid Tumours, Version 1.1; *RET*: rearranged during transfection; SAS: Supplemental Analysis Set; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3; SCE: Summary of Clinical Efficacy; US: United States.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off),[76] Drilon et al. 2020b.[83] Drilon et al. 2022.[80]

Summary of clinical data cut-off dates

An analysis was conducted for 837 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 13th January 2023 data cut-off. Unless noted otherwise, the results presented and analysed in this submission are based on this data cut-off. The safety evaluable data set includes all 837 patients treated with selpercatinib as of the 13th January 2023 data cut-off.[80]

Statistical methods

Table 11: Statistical methods for the primary analysis of LIBRETTO-001

Trial name	LIBRETTO-001
Hypothesis objective	**Phase I:** • The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib **Phase II:** • The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	• Efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyse. • The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the Investigator are presented in Appendix L.2. • For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response. • Best overall response was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e. the crude proportion of patients with best overall response of CR or PR) . • Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions. • The estimate of the ORR was accompanied by 2-sided 95% exact binomial confidence intervals (CI). • To assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analyses were performed (see Table 10). These analyses were conducted in all the analysis sets.
Sample size, power calculation	**Phase I** • The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1–8), a total of approximately 120 patients would be enrolled in Phase I.

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

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

Abbreviations: AE: adverse event; BOR: best overall response; CI: confidence interval; CR: complete response; DLT: dose limiting toxicity; DOR: duration of response; IRC: Independent Review Committee; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; MTD: maximum tolerated dose; ORR: objective response rate; OS: overall survival; *RET*: rearranged during transfection; PFS: progression-free survival; PK: pharmacokinetic; PR: partial response; RP2D: recommended Phase II dose; SRC: Safety Review Committee.
Source: Drilon et al. 2020b.[83]

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib in previously treated patients with *RET* fusion-positive NSCLC. Definitions for these outcome measures are presented in Table 12.

Table 12: 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:[90] • **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. • **Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. • **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). • **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Secondary outcomes	
Duration of response	DOR was calculated for patients who achieved either a CR or PR. For such patients, DOR was defined as the number of months from the start date of CR or PR (whichever response was observed first) and the first date that recurrent or progressive disease was objectively documented. If a patient died, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death was used to denote the response end date.
Progression free survival	PFS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented progressive disease, as per RECIST v1.1 or death (whatever the cause).
Overall survival	OS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause).
EORTC QLQ-C30	The EORTC QLQ-C30 is a validated instrument that assesses HRQoL in adult cancer patients. It includes a total of 30 items and is composed of scales that evaluate physical (5 items), emotional (4 items), role (2 items), cognitive (2 items) and social (2 items) functioning, as well as global health status (2 items). Higher mean scores on these scales represent better functioning. There are also 3 symptom scales measuring nausea and vomiting (2 items), fatigue (3 items) and pain (2 items), and 6 single items assessing financial impact and various physical symptoms. Higher mean

	scores on these scales represent better functioning or greater symptomology. EORTC QLQ-C30 subscale scores range from 0 to 100. Descriptive analyses reported median/quartile, mean/standard deviation and mean change/standard error from baseline for each subscale at each study visit. A minimal clinically meaningful difference was defined as at least a 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[91] Patients with "improvement" were defined as those who demonstrated a ≥10-point improvement from their baseline score. Patients with "worsening" were defined as those who demonstrated a deterioration by ≥10-points from their baseline score. A sustained change (improvement or worsening) was defined as an improvement or worsening, respectively, (as defined above) without any further change in score ≥10 points.

Abbreviations: BOR: best overall response; CR: complete response; DOR: duration of response; EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: Drilon et al. 2020b.[83]

B.2.5 *Critical appraisal 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.

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

Table 13: Quality assessment results for the LIBRETTO-001 trial

Study Question (Yes/No/Unclear)	Grade (yes/no/unclear)
1. Did the study address a clearly focussed issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib in patients with advanced solid tumours including *RET* fusion-positive solid tumours. The primary endpoint of Phase I was MTD and/or the RP2D of selpercatinib. The primary endpoint of Phase II was ORR and secondary endpoints include DOR, PFS and OS.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined in Drilon *et al.* 2020b and reported in Table 5.[83] However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes. This was a prospective study with an appropriate study design with validated tools for outcome assessment and data collection. All patients were classified using the same criteria.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1 and assessed by an IRC. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.

5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No. Confounding factors were not listed, however, baseline characteristics are extensively reported (see Section B.2.3.3).
5B. Have they taken account of the confounding factors in the design and/or analysis?	The study has no control arm, therefore randomisation or stratification are not applicable.
6A. Was the follow up of subjects complete enough?	Yes. Out of the 247 subjects enrolled in the treatment-exposed (IAS) cohort of LIBRETTO-001, a high proportion of patients ([redacted]) were continuing treatment at the latest data cut-off.[76, 80]
6B. Was the follow up of subjects long enough?	The follow-up of subjects was long enough to collect a sufficient number of PFS and OS events and estimate the median for each of these outcomes.
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked anti-tumour activity in previously treated patients with *RET* fusion-positive NSCLC, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with RECIST assessment used on all scans to determine the ORR with an IRC. Response was confirmed by a repeat assessment no less than 28 days later.
9. Do you believe the results?	Yes. The primary endpoint for Phase II (ORR) aligns with published results from trials for other *RET* selective inhibitors.[92]
10. Can the results be applied to the local population?	Yes. These results can be applied to previously treated patients with *RET* fusion-positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.[92] ORR was 63.5% (n=148) in previously treated NSCLC patients who received pralsetinib in a Phase 1/2 trial compared to 61.5% in the LIBRETTO-001 study.[93]
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first and subsequent lines of therapy.

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

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of clinical effectiveness results

- Overall response rate (ORR) represented the primary outcome of the LIBRETTO-001 trial. Selpercatinib treatment resulted in high tumour response rates in treatment-exposed *RET* fusion-positive NSCLC patients, decreasing tumour size and delaying disease progression for most patients: ORR was 61.5% (152/247, 95% CI: 55.2–67.6) in the IAS population.[76]
- At the time of data cut-off (13th January 2023), the median DOR was 31.6 months (95% CI: 20.4–42.3) in the IAS population, with PD observed in [redacted]247[redacted] patients at a median follow-up of 39.5 months.[76]
- The median PFS by IRC assessment was 26.2 months (95% CI: 19.3–35.7) in the IAS population. Within the IAS population, death or disease progression was reported in [redacted]247 ([redacted]%) patients at a median follow-up of 41.2 months.[76] As progressed disease is associated with reduced patient HRQoL, these results indicate that selpercatinib treatment could bring

positive benefits to treatment-exposed *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their HRQoL for longer.[18]
- The median OS was 47.6 months in the IAS population, with the majority of patients ([redacted]247; [redacted]%) remaining alive at a median follow-up of 44.6 months.
- Patient reported outcomes were assessed using the EORTC QLQ-C30 in the IAS population. Patients did not experience a notable change in QLQ-C30 subscale scores compared to baseline by the end of treatment with selpercatinib (±10 points from baseline as per scale definition of improvement or worsening). The mean change from baseline scores (standard deviation [SD]) at the end of treatment for [redacted]247 previously-treated patients were [redacted] ([redacted]) for emotional, [redacted] ([redacted]) for physical, [redacted] ([redacted]) for role and [redacted] ([redacted]) for social functioning scales.
- Overall, at the data cut-off, the majority of previously treated advanced *RET* fusion-positive NSCLC patients had experienced improvements in quality of life as determined by QLQ-C30 subscales across the treatment period with selpercatinib
- The results of LIBRETTO-001 trial demonstrate that treatment with selpercatinib results in a high and durable response rate for treatment-experienced *RET* fusion-positive NSCLC patients, corresponding with maintenance of patients' HRQoL and prolonged survival

The clinical effectiveness results in the IAS trial population, assessed by IRC, are presented Section B.2.6.1–B.2.6.5 below. Results from the Investigator assessment are available in Appendix L.2. As of the 13th January 2023 data cut-off, the 247 patients in the IAS had a median follow-up of 39.5 months (interquartile range [IQR]: [redacted]).[76] Real-world data from patients with *RET* fusion-positive NSCLC in UK clinical practice are available via the SACT cohort and are presented in the reference pack.[4] As selpercatinib has been available via the CDF in this indication only since 2022, these data are currently not sufficiently mature to inform this submission. In addition to this short follow-up, the majority of patients are still on treatment – at the latest DCO, only [redacted]% (n=[redacted]) patients were identified as no longer being on treatment. As such, the pivotal clinical trial, LIBRETTO-001, provides the data that inform the cost-effectiveness analysis presented in this submission.[76]

B.2.6.1 Primary endpoint: objective response rate

ORR was defined as the proportion of patients with a BOR of confirmed CR or PR based on RECIST v1.1 (see Table 5, Section B.2.3.2). In the IAS trial population, the ORR was 61.5% (152/247, 95% CI: 55.2–67.6) as per IRC assessment (Table 14). Based on BOR, 32.4% of patients in the IAS population were assessed to have stable disease, whilst the majority were assessed to have a partial response (53.4%). Only 7 patients (2.8%) were assessed to have progressive disease as BOR.[76]

Lesion measurement data are available for [redacted] of the 247 patients in the IAS because [redacted] patients were excluded: [redacted] patients did have non-target lesions only and [redacted] did not have post-baseline target lesion measurement. In these [redacted] patients, individual patient responses to selpercatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, show that tumour diameter had decreased in the vast majority of patients at the latest data cut-off (Figure 5). These results indicate that selpercatinib treatment results in high response rates in treatment-exposed patients with *RET* fusion-positive NSCLC, delaying disease progression and decreasing tumour size.

Table 14: BOR and ORR for treatment-exposed *RET* fusion-positive NSCLC patients (IAS; IRC assessment)

Criteria	IAS (treatment-exposed; N=247)
Best overall response, n (%)	

Complete response	20 (8.1)
Partial response	132 (53.4)
Stable disease	80 (32.4)
Progressive disease	7 (2.8)
Not evaluable	8 (3.2)
Objective response rate (CR + PR)	
n (%)	152 (61.5)
95% CI	55.2–67.6

Abbreviations: BOR: best overall response; CI: confidence interval; CR: complete response; IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; ORR: objective response rate; PR: partial response; RET: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.1 and Table JZJA.8.35.[76]

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

Footnotes: Dotted lines indicate thresholds for partial response and progressive disease. A decrease in tumour size of ≥30% was considered a partial response, whilst an increase in tumour size of ≥20% was considered progressive disease. For each patient, the best percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. 21 patients are not included because 16 patients have non-target lesions only and five do not have postbaseline target lesion measurement.
Abbreviations: IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; RET: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Figure JZJA.5.4.[76]

B.2.6.2 Secondary endpoint: duration of response

For assessment of DOR, time until occurrence of an event was measured. An event was recorded as death or disease progression in a patient. Patients were censored as per the criteria listed in Table 11 (Section B.2.4).

Of the 152 patients in the IAS trial population who responded to treatment with selpercatinib, at the data cut-off, [redacted] patients were alive with no documented disease progression. The median DOR by IRC assessment was 31.6 months (95% CI: 20.4–42.3) in the IAS population (Table 15).[76] As of the 13th January 2023 data cut-off, [redacted] patients had maintained a response for ≥12 months in the IAS population.[76]

By Kaplan-Meier estimate, the probability of remaining in response at 6 months was [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]) at 12 months for the IAS population.[76] These results indicate that patient benefit from a decrease in tumour size is durable, with almost all patients predicted to maintain their response for 6 months, and approximately three-quarters of patients anticipated to remain in response for at least 12 months ([redacted]%). The Kaplan-Meier plot of DOR is presented in Figure 6.

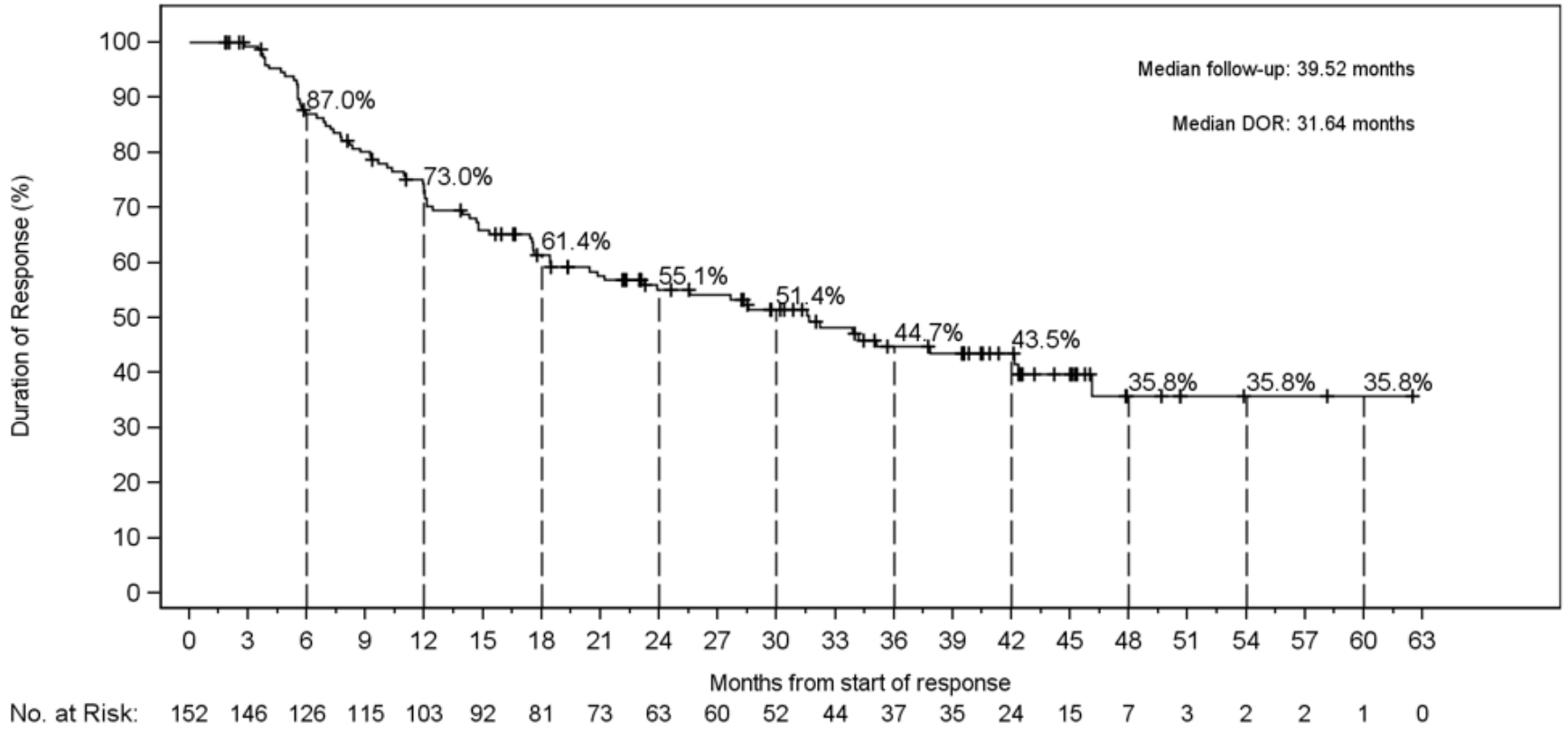
Table 15: DOR for treatment-exposed *RET* fusion-positive NSCLC patients (IAS; IRC assessment)

Criteria	IAS (treatment-exposed; N=247)
Patients with response	152
Response status, n (%)[a]	
Disease progression	[redacted]
Death	[redacted]
Censored	75 (49.3)
Reason censored, n (%)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without documented PD	[redacted]
Discontinued from study without documented PD	[redacted]
Died or documented PD after missing 2 or more consecutive visits	[redacted]
Discontinued treatment and lost to follow-up	[redacted]
DOR (months)[b,c]	
Median	31.6
95% CI	20.4–42.3
Minimum-maximum	[redacted]
Rate (%) of DOR[b,d]	
≥12 months (95% CI)	[redacted]
≥24 months (95% CI)	[redacted]
≥36 months (95% CI)	[redacted]
≥48 months (95% CI)	[redacted]

≥60 months (95% CI)	[redacted]
DOR follow-up (months)[b]	
Median	39.52
25th, 75th percentiles	[redacted]
Observed DOR, n (%)[b]	
<6 months	[redacted]
≥6 to 12 months	[redacted]
≥12 to 18 months	[redacted]
≥18 to 24 months	[redacted]
≥24 months	[redacted]

Footnotes: [a]Status as of the patient's last disease assessment 13th January 2023. [b]Estimated based on Kaplan-Meier method. [c]95% CI was calculated using Brookmeyer and Crowley method. [d]95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; DOR: duration of response; IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; PD: progressed disease
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.1. and Table JZJA.8.37.[76]

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



Footnotes: Censored patients denoted by "+".
Abbreviations: DOR: duration of response; IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; RET: rearranged during transfection
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Figure JZJA.5.2.[76]

B.2.6.3 Secondary endpoint: progression free survival

PFS was derived for each patient as the number of months from the date of the first dose of the study drug until documented disease progression or death due to any cause. Patients were censored as per the criteria listed in Table 5 (Section B.2.3.2).

As of the 13th January 2023 data cut-off, in the IAS population, [redacted] ([redacted]%) patients were alive and without documented PD, with a median duration of PFS of 26.15 months (95% CI: 19.3–35.7).[76] Death or disease progression was reported in [redacted]247 ([redacted]%) of patients at a median follow-up of 41.20 months (Table 16).[76]

By Kaplan-Meier estimate, the probability of patients in the IAS population being progression-free at 6- and 12- months or more was 83.7% and 70.6%, respectively, by IRC assessment.[76] These results indicate that administration of selpercatinib can produce clinically meaningful responses for a high proportion of treatment-exposed patients, with approximately two-thirds estimated to be event-free (death or disease progression) for at least a year after receiving their first dose (70.6%). The Kaplan-Meier plot of PFS for the IAS population is presented in Figure 7.[76]

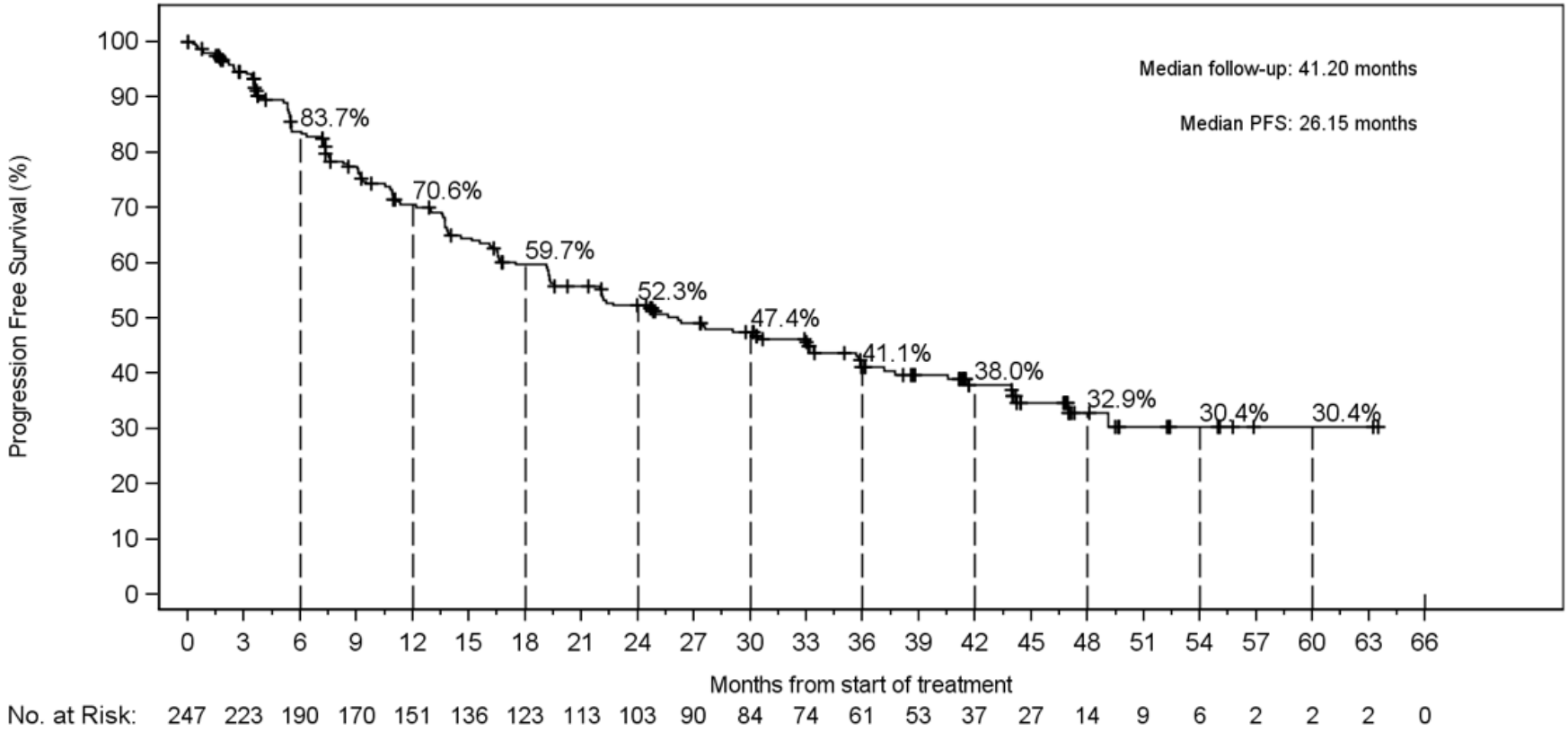
Table 16: PFS for treatment-exposed *RET* fusion-positive NSCLC patients (IAS; IRC assessment)

Criteria	IAS (treatment-exposed; N=247)
Progression status, n (%)[a]	
Disease progression	[redacted]
Death (no disease progression beforehand)	[redacted]
Censored	114 (46.2)
Reason censored, n (%)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without documented PD	[redacted]
Discontinued from study without documented PD	[redacted]
Died or documented PD after missing 2 or more consecutive visits	[redacted]
Discontinued treatment and lost to follow-up	[redacted]
Duration of PFS (months)[b,c]	
Median	26.15
95% CI	19.3–35.7
Minimum-maximum	[redacted]
Rate (%) of PFS[b,d]	
≥12 months (95% CI)	70.6[redacted]
≥24 months (95% CI)	52.3[redacted]
≥36 months (95% CI)	41.1 (34.2–47.9)
≥48 months (95% CI)	32.9[redacted]
≥60 months (95% CI)	30.4[redacted]
Duration of PFS follow-up (months)[b]	
Median	41.20

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

Footnotes: [a]Status as of the patient's last disease assessment on or before 13th January 2023. [b]Estimated based on Kaplan-Meier method (+ = censored observation). [c]95% CI was calculated using Brookmeyer and Crowley method. [d]95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; PD: progressed disease; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.3.[76]

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



Footnotes: Censored patients denoted by "+".
Abbreviations: IAS: integrated analysis set; IRC: independent review committee; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RET: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Figure JZJA.5.6.[76]

B.2.6.4 Secondary endpoint: overall survival

For assessment of OS, the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause) was recorded. Patients who were alive or lost to follow-up as of the data cut-off date were right-censored (see detailed censoring criteria listed in Table 11 (Section B.2.4). The censoring date was determined from the date the patient was last known to be alive.

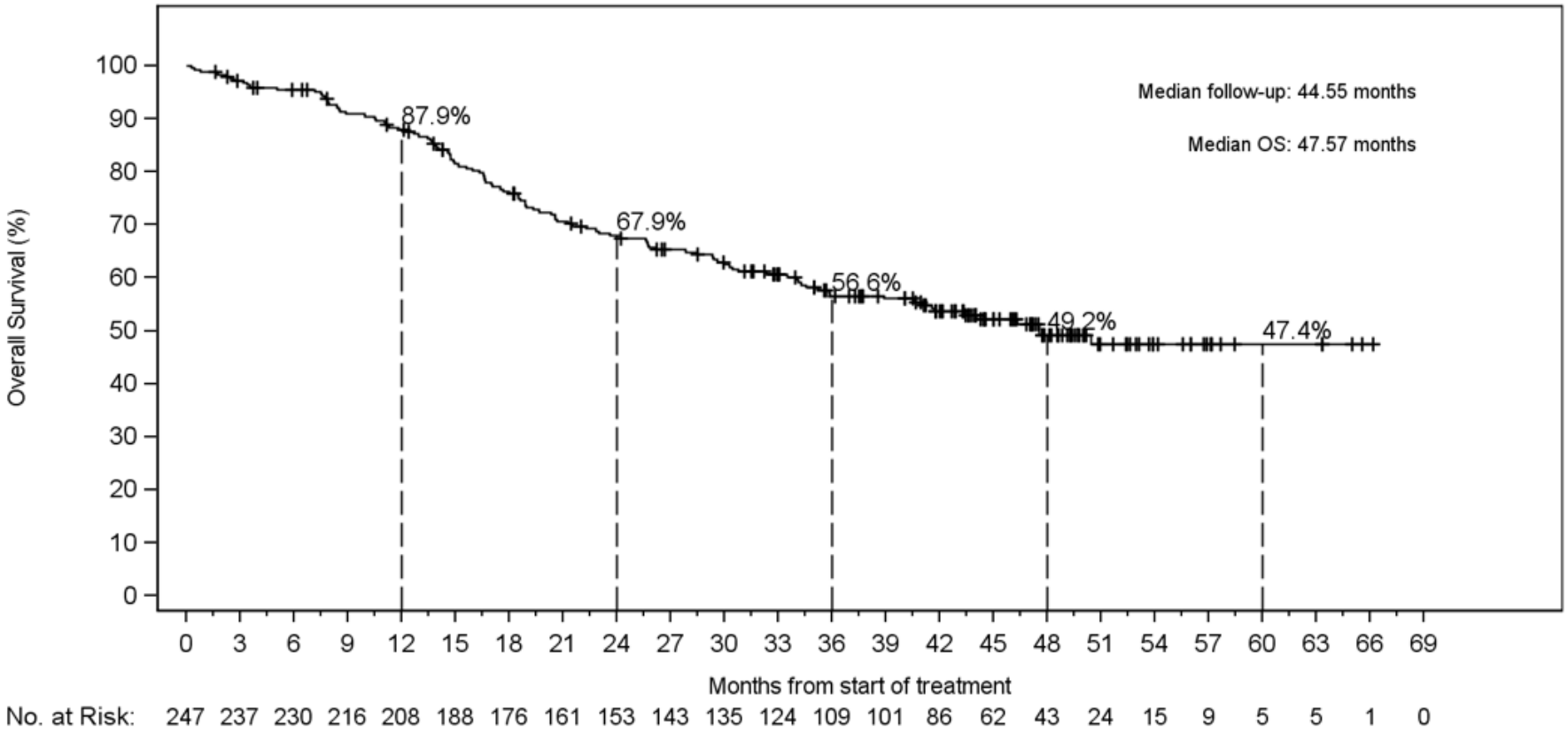
The median OS in the IAS trial population was 47.6 months (95% CI: 35.9–NE) at the 13th January 2023 data cut-off, with the majority of patients (137/247; [redacted]%) remaining alive at a median follow-up of 44.6 months. At 12 months, the OS rate was 87.9% (95% CI: [redacted]) for the IAS population and 67.9% (95% CI: [redacted]) at 24 months, providing evidence to support that selpercatinib will result in an extension to patients' lives (Table 17).[76] The Kaplan-Meier plot for OS in the IAS population is presented in Figure 8.

Table 17: OS for treatment-exposed *RET* fusion-positive NSCLC patients (IAS)

Criteria	IAS (treatment-exposed; N=247)
Survival status, n (%)[a]	
Died	[redacted]
Censored	[redacted]
Overall survival (months)[b, c]	
Median	47.57
95% CI for median	35.9–NE
Min – max	[redacted]
Duration of follow-up (months)[c]	
Median	44.55
25th, 75th percentiles	[redacted]
Rate (%) of overall survival[b, d]	
≥12 months (95% CI)	87.9[redacted]
≥24 months (95% CI)	67.9[redacted]
≥36 months (95% CI)	56.6 (49.8–62.8)
≥48 months (95% CI)	49.2[redacted]
≥60 months (95% CI)	47.4[redacted]

Footnotes: [a]Status as of the patient's last disease assessment on or before 13th January 2023. [b]Estimated based on Kaplan-Meier method (+ = censored observation). [c]95% CI was calculated using Brookmeyer and Crowley method. [d]95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; IAS: integrated analysis set; NE: not estimable.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.4. and Table JZJA.8.47.[76]

Figure 8: Kaplan-Meier plot of OS for treatment-exposed *RET* fusion-positive NSCLC (IAS)



Footnotes: Censored patients denoted by "+".
Abbreviations: IAS: integrated analysis set; NSCLC: non-small cell lung cancer; OS: overall survival; RET: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Figure JZJA.5.8.[76]

B.2.6.5 EORTC QLQ-C30

As of the 13th January 2023 data cut-off, [redacted]247 patients in the IAS trial population had completed a baseline assessment as part of a "QLQ-C30 Analysis Set" and at least one following assessment. EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks during the first year, at visit 13 and then every 12 weeks until the end of treatment visit, and then at the follow-up visit after treatment discontinuation (see Table 5, Section B.2.3.2 for further details of EORTC QLQ-C30 methodology).[85]

By the end of treatment (EOT), of the [redacted] patients who completed the assessments, [redacted] experienced meaningful improvements (of at least 10 points) in the global health status/QoL subscale. With regards to physical, emotional, role and cognitive function, [redacted], [redacted], [redacted] and [redacted] of patients, respectively, reported meaningful improvements at the EOT with selpercatinib. Improvements were also seen in the EORTC QLQ-C30 subscales testing symptomology and financial impact of the disease by the EOT with selpercatinib. Of the [redacted] patients who completed the assessments, [redacted] reported an improvement in nausea and vomiting, [redacted] in fatigue, [redacted] in pain, [redacted] in dyspnoea, [redacted] in insomnia, [redacted] in appetite loss, [redacted] in constipation, [redacted] in diarrhoea and [redacted] in financial difficulties (see Appendix L.1).

The mean change from baseline scores (SD) at the EOT for [redacted]247 of patients from the IAS for emotional functioning, physical functioning, role functioning and social functioning subscales were not notably different (±10 points from baseline as per scale definitions for improvement and worsening): [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]) and [redacted] ([redacted]), respectively. Overall, at the data cut-off, the majority of previously treated advanced *RET* fusion-positive NSCLC patients had experienced improvements in quality of life across the period of treatment with selpercatinib as determined by QLQ-C30 subscales.

B.2.7 *Subgroup analysis*

Owing to the high prevalence of brain metastases in *RET* fusion-positive NSCLC patients, the efficacy of selpercatinib in the subset of patients with brain metastases was investigated. A total of 77 (31.2%) of the 247 previously treated patients in the IAS population had Investigator assessed CNS metastases at baseline.[76] The median duration of PFS assessed by the IRC for patients with NSCLC and CNS metastasis (N=107) was [redacted]) and the median duration of follow-up was [redacted] months ([redacted]).

26 patients with NSCLC (regardless of treatment history) had measurable CNS disease at baseline as assessed by IRC. Patients with measurable CNS lesions had a CNS ORR of 84.6% (22/26; [redacted]), demonstrating efficacy of selpercatinib against CNS metastases (Table 18).

Table 18: CNS ORR and DOR by IRC assessment in *RET* fusion-positive treatment-exposed patients with measurable CNS lesions

	NSCLC with Prior RT			NSCLC without Brain RT (N=[redacted])	All NSCLC (N=26)
	Brain RT ≤2 Months Prior to First Dose (N=[redacted])	Brain RT >2 Months Prior to First Dose (N=[redacted])	All NSCLC with Prior RT (N=[redacted])		
CNS Objective Response Rate[a] (CR + PR)					
Number of Patients with CR + PR (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	22 (84.6)
95% CI[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNS Clinical Benefit Rate					
Number of Patients with CR + PR + SD[c] (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNS Duration of Response (months)[d,e]					
No. of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (18.2)
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	9.36 (7.4–15.3)
Minimum–Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]CNS ORR is defined as the proportion of patients with best overall response of CR or PR. Response was confirmed by a repeat assessment no less than 28 days. [b]95% CI was calculated using Clopper-Pearson method. [c]Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [d]Estimate based on Kaplan-Meier method. +Censored observation.
Abbreviations: CI: confidence interval; CNS: central nervous system; CR: complete response; DOR: duration of response; IRC: Independent Review Committee; N: number of patients; n: number of patients in specific category; NE: not estimable; No: number; NR: not reported; NSCLC: non-small cell lung cancer; ORR: objective response rate; PR: partial response; RET: rearranged during transfection; RT: radiation therapy.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.5.[76]

B.2.8 *Meta-analysis*

As LIBRETTO-001 is a single arm trial, it is not possible to conduct any form of meta-analysis. A network meta-analysis (NMA) has been conducted, as reported in Section B.2.9.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect treatment comparisons

Methodology

- A network meta-analysis (NMA) was performed to compare the efficacy of selpercatinib to other second line treatments relevant to the decision problem for the outcomes of ORR, PFS and OS. The methodology of the ITC is consistent with the NICE Committee preferences and accepted approach in TA760.[2]
- LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced *RET* fusion-positive NSCLC directly to comparators relevant to the decision problem.
- In order to include the IAS trial population data from LIBRETTO-001 in the NMA it was therefore necessary to generate a pseudo-control arm.
- Individual patient data (IPD) from the docetaxel plus placebo chemotherapy arm of the REVEL trial (which compared efficacy of ramucirumab plus docetaxel vs docetaxel plus placebo in patients with pre-treated, metastatic NSCLC) were used to generate a pseudo-control arm. The LIBRETTO-001 selpercatinib arm and the docetaxel plus placebo chemotherapy arm underwent propensity score matching (PSM) to account for any differences between trial populations, but did not adjust for *RET* fusion status.
- A random effects model with informative priors was used for all outcomes.

Results

- Treatment with selpercatinib resulted in higher odds of ORR when compared to nintedanib plus docetaxel chemotherapy (OR [95% CrI]: [redacted]) and docetaxel monotherapy (OR [95% CrI]: [redacted]), respectively.
- In addition, treatment with selpercatinib and had a lower hazard of progression or death (PFS) compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted]) and docetaxel monotherapy (HR [95% CrI]: [redacted]), respectively.
- Similarly to PFS, treatment with selpercatinib and demonstrated a lower risk of death (OS) when compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted]) and docetaxel monotherapy (HR [95% CrI]: [redacted]), respectively.

Uncertainties in the indirect treatment comparison

- As the only study from which IPD was available, the REVEL trial represented the only option to inform the pseudo-comparator arm of the ITC. However, the docetaxel plus placebo arm of REVEL may have overestimated the efficacy of docetaxel due to the possibility that some patients experienced a placebo effect.
- The process of generating a pseudo-comparator arm to connect selpercatinib to the NMA was likely to be associated with inherent uncertainty. However, heterogeneity in patient baseline characteristics between LIBRETTO-001 and REVEL was adjusted for via a PSM to minimise any associated uncertainty.
- There were noticeable differences in the baseline characteristics of the studies included in the NMA including age, sex, proportion of Asian patients and the date of publication of the study. These differences may result in uncertainty in the estimates of treatment effect. However, a meta-regression was explored to assess the impact of these differences in the baseline characteristics on the NMA.
- To minimise potential biases, the analysis used multiple methods recommended by NICE and the most robust statistical techniques for ITCs. Overall, the analyses presented provide evidence of the relative efficacy of selpercatinib in previously treated patients with NSCLC given the limitations of existing data.

Conclusion

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

LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced *RET* fusion-positive NSCLC directly to comparators relevant to the decision problem. In order to generate relative efficacy estimates for selpercatinib versus comparators of interest, it was therefore necessary to conduct an indirect treatment comparison. The methodology of the ITC was consistent with the NICE Committee preferences and accepted approach in TA760.[2]

The indirect treatment comparison comprised two steps:

1. Generation of a pseudo-control arm to selpercatinib through propensity score matching between the selpercatinib arm of LIBRETTO-001 and the docetaxel plus placebo chemotherapy arm of the REVEL RCT
2. Adjoining of selpercatinib to an NMA of second-line NSCLC treatments via the pseudo-control arm

B.2.9.1 Generation of the pseudo-comparator arm

The pseudo-control arm was simulated for the LIBRETTO-001 trial using IPD available for the docetaxel chemotherapy plus placebo arm from the REVEL RCT. REVEL included patients with advanced, squamous or non-squamous NSCLC who had progressed after a first-line platinum-based chemotherapy regimen.[94] Control IPD were not available from any other trial identified in the SLR.

Propensity score matching was conducted between IPD from the IAS population of LIBRETTO-001 and the docetaxel chemotherapy plus placebo arm from the REVEL in order to account for differences in the two trial populations.

Propensity score matching approach

Current statistical methods that match one trial to another through use of IPD rely on the presence of some overlap in baseline population characteristics, particularly those that may have a prognostic impact on trial endpoints (e.g. smoking). Propensity score matching uses IPD from one data set to match to another data set. The propensity score for an individual is defined as the probability that the individual receives the treatment, given all the confounding covariates which are being controlled for in the analysis.[95] Specifically, matching aims to replicate randomisation by identifying control individuals who are similar to the treated individuals in one or more characteristics.[96] By matching the outcomes of individuals who differ in the treatment variable, but are otherwise observationally similar, this approach enables estimation of a treatment effect between the interventions under investigation.[96]

Differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the docetaxel chemotherapy plus placebo arm from REVEL were adjusted for using propensity score estimated using a multivariable logistic regression approach.[95] The IPD from both trials were used to adjust for between-trial differences in observed baseline characteristics known to have an impact on prognosis (e.g., smoking status, sex) and to assess outcomes in a matched population. Guidance provided in NICE TSD17 informed the propensity score matching process.[96]

The covariates that were used as adjustment factors during propensity score matching are summarised in Table 19. The matching process better aligned key population characteristics between the selpercatinib and pseudo-control arm. Adjustments relating to the presence of *RET* fusion were not made, due to the inconclusive prognostic nature of a *RET* fusion, as described in Section B.1.3.1. The prognostic variables used in the propensity score matching have been validated by a UK expert clinician as the most clinically relevant factors for adjustment, and this is in line with the conclusions of the NICE Committee in the previous appraisal of selpercatinib in this indication.[2, 6] In order to have data that allowed for matching, [redacted] patients from the LIBRETTO-001 dataset were excluded from the analysis: 7 had ECOG PS 2 at baseline, [redacted] patients did not have non-squamous disease, and [redacted] patients with missing race data. In the REVEL trial, 625 patients were allocated to the docetaxel chemotherapy plus placebo arm, with 618 patients receiving the assigned treatment. Of these patients, 447 were confirmed to have non-squamous disease and were used to generate the pseudo-control arm.

Table 19: Summary of patient characteristics of the REVEL and LIBRETTO-001 trial populations

Characteristic	Baseline characteristics		
	LIBRETTO-001 (selpercatinib; N=[redacted])	Before PSM	After PSM[a]
		REVEL (docetaxel + placebo; N=447)	REVEL (docetaxel + placebo; N=234)
Age (mean, years)	[redacted]	59.82	59.00
ECOG PS = 1, %	[redacted]	68.3%	61.5%
Female, %	[redacted]	38.4%	46.2%
Never smoked, %	[redacted]	25.9%	48.3%
Race: Asian, %	[redacted]	14.2%	26.1%
Race: Other[b], %	[redacted]	6.7%	11.1%
Stage III, %	[redacted]	8.9%	6.4%
Stage IV, %	[redacted]	86%	91.9%
Time since diagnosis to start of trial, median months	[redacted]	12.04	15.12

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

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% credible intervals (CrIs) for selpercatinib versus the pseudo-control arm (Table 20). The hazard ratio was then introduced into the NMA for each outcome.

Table 20: Estimated treatment effects for selpercatinib versus docetaxel chemotherapy plus placebo (pseudo-control arm)

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

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

The Kaplan-Meier outputs for PFS and OS, from adjustment for prognostic factors through matching using propensity scores, are presented in Figure 9 and Figure 10, respectively.

Figure 9: Kaplan-Meier charts for PFS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients following propensity score matching

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

Figure 10: Kaplan-Meier charts for OS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients following propensity score matching

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

B.2.9.2 NMA methodology

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

The original SLR was conducted in September 2019, and subsequently underwent three updates in October 2020, July 2021 and January 2024 with the aim of identifying relevant clinical evidence for the efficacy and safety of selpercatinib or relevant comparators in treatment-experienced patients with locally advanced or metastatic non-squamous NSCLC receiving second-line treatment (see Section B.2.1 and Appendix D).

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

Of the 165 studies available for meta-analysis up until the January 2024 update, 30 were connected and could be analysed in the NMA. As described in B.2.9.1, generation of the pseudo-comparator arm enabled selpercatinib to be adjoined to the NMA and therefore relative treatment effects estimated between selpercatinib and relevant comparators. The full methodology of this NMA is provided in Appendix D.

B.2.9.3 Indirect treatment comparison results

For ORR, the proportion of patients who experienced an objective response was modelled and treatment effect estimates were presented as OR with associated 95% CrIs. For OS and PFS, HRs representing treatment effect estimates with corresponding standard error values were synthesised in the model. For all outcomes, a random effects model (using informative priors) was performed.

Overall response rate

The network diagram for ORR is presented in Figure 11.

Figure 11: Network diagram for treatments included in the NMA for ORR

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

The relative treatment effect estimate (OR) for ORR for comparators of interest versus docetaxel monotherapy chemotherapy are presented in Table 21. An OR>1 is indicative of better response for the treatment in the row versus the reference treatment in the column. Treatment with selpercatinib (OR [95% CrI]: [redacted]) and nintedanib plus docetaxel chemotherapy (OR [95% CrI]: [redacted]) resulted in higher odds of ORR when compared to docetaxel monotherapy. In addition, both nintedanib plus docetaxel chemotherapy and docetaxel monotherapy had lower odds of overall response when compared to selpercatinib (Table 22).

Table 21: Relative treatment effect estimates expressed as pairwise ORs versus docetaxel monotherapy (with 95% CrI) for ORR, random effects model with informative priors

Treatment	Pairwise OR (95% CrI) versus docetaxel monotherapy
Selpercatinib	[redacted]
Nintedanib plus docetaxel	[redacted]

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

Table 22: Relative treatment effect estimates expressed as pairwise ORs versus selpercatinib (with 95% CrI) for ORR, random effects model with informative priors

Treatment	Pairwise OR (95% CrI) versus selpercatinib
Docetaxel monotherapy	[redacted]
Nintedanib plus docetaxel	[redacted]

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

Progression-free survival

The network diagram for PFS is shown in Figure 12.

Figure 12: Network diagram for treatments included in the NMA for PFS

Abbreviations: NMA: network meta-analysis; PD-L1: programmed cell death ligand-1; PFS: progression-free survival.

The relative treatment effect estimates for interventions of interest for PFS versus docetaxel chemotherapy are presented in Table 23. A HR<1 is indicative of a lower hazard of progression or death compared to the reference treatment. Treatment with both selpercatinib (HR [95% CrI]: [redacted]) and nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted]) had a lower hazard of progression or death compared to docetaxel monotherapy. In addition, both docetaxel monotherapy and nintedanib plus docetaxel chemotherapy were associated with a higher hazard of progression or death when compared to selpercatinib (Table 24).

Table 23: Relative treatment effect estimates expressed as HRs versus docetaxel monotherapy (with 95% CrI) for PFS, random effects model with informative priors

Treatment	Pairwise median HR (95% CrI) versus docetaxel monotherapy
Selpercatinib	[redacted]
Nintedanib plus docetaxel	[redacted]

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

Table 24: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for PFS, random effects model with informative priors

Treatment	Pairwise median HR (95% CrI) versus selpercatinib
Docetaxel monotherapy	[redacted]
Nintedanib plus docetaxel	[redacted]

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

Overall survival

The network diagram for OS is shown in Figure 13.

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

Footnotes: Line thickness represents the number of studies comparing two given treatments and circle radius represents the number of studies with the given treatment arm.
Abbreviations: NMA: network meta-analysis; OS: overall survival; PD-L1: programmed cell death ligand-1.

The relative treatment effect estimates for interventions of interest for OS versus docetaxel monotherapy are presented in Table 25.

A HR<1 is indicative of a lower hazard of progression or death compared to the reference treatment. Treatment with both selpercatinib (HR [95% CrI]: [redacted]) and nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted]) had a lower hazard of death when compared to docetaxel monotherapy. In addition, as with PFS, both docetaxel monotherapy and nintedanib plus docetaxel chemotherapy were associated with a higher hazard of death when compared to selpercatinib (Table 26).

Table 25: Relative treatment effect estimates expressed as HRs versus docetaxel monotherapy (with 95% CrI) for OS, random effects model with informative priors

Treatment	Pairwise median HR (95% CrI) versus docetaxel monotherapy
Selpercatinib	[redacted]
Nintedanib plus docetaxel	[redacted]

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

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

Treatment	Pairwise median HR (95% CrI) versus selpercatinib
Docetaxel monotherapy	[redacted]
Nintedanib plus docetaxel	[redacted]

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

B.2.9.4 Meta-regression

Several key areas of heterogeneity were identified between trials included in the NMA including baseline characteristics (ECOG PS), sex distribution and proportion of Asian patients. To assess the impact of this between trial heterogeneity on the trial results, a meta-regression was performed to adjust for baseline characteristics between included studies. Various covariates including mean age, the proportion of patients with ECOG score of 1, the proportion of patients who were male, the initial year of publication and the proportion of Asian patients were included one at a time to assess whether they improved model fit. The analyses were performed for ORR, OS and PFS. Models related to age (for OS and PFS) and year of initial publication (OS) were the only models to converge. Random-effect (± informative priors) models were considered for all endpoints (ORR, PFS, OS).

B.2.9.5 Assessment of inconsistency

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

The results of the inconsistency assessment are provided in Table 27 below. An assessment of inconsistency between direct and indirect evidence in the network was conducted for the connected network. As the network was relatively sparse and had only few loops of evidence for evaluation of consistency, the results were inconclusive. The direct and indirect evidence available in the network shows that the analysis for OS and PFS might be affected by

inconsistency of evidence since the DICs for inconsistency models were [redacted] and [redacted] units lower respectively than for consistency models. For ORR, the DIC for inconsistency model was [redacted] units lower than for consistency model. Therefore, inconsistency is expected to impact the ORR analysis to a lesser extent than the analyses for OS and PFS.

Table 27: Result of inconsistency assessment on the NMAs (random effects with informative priors)

Analysis	Consistency model		Inconsistency model		Number of data points
	Dbar	DIC	Dbar	DIC	
OS	[redacted]	[redacted]	[redacted]	[redacted]	32
PFS	[redacted]	[redacted]	[redacted]	[redacted]	33
ORR	[redacted]	[redacted]	[redacted]	[redacted]	38

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

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

Due to the single-arm nature of the LIBRETTO-001 trial, it was necessary to generate a pseudo-comparator arm in order to connect selpercatinib to the NMA, a process that is associated with inherent uncertainty. IPD from the docetaxel chemotherapy plus placebo arm of REVEL were utilised to inform the control arm and propensity score matching undertaken to account for differences in the trial populations. The choice of studies to inform a pseudo-comparator arm in the NMA was limited to REVEL, as it was the only study with IPD available for patients with previously-treated, advanced NSCLC. However, the efficacy of docetaxel plus placebo may be overestimated by the REVEL study due to some patients experiencing a placebo effect.

Adjustment for the presence of *RET* fusion was not made owing to the inconclusive prognostic nature of *RET* (as discussed in Section B.1.3.1) and the increased uncertainty these adjustments would bring to the analyses. The prognostic nature of *RET* has been explored in a large US-based study, which found that after adjustment of baseline covariates, there was no significant difference in PFS and OS between patients with *RET* fusions and patients without, providing evidence that *RET* fusion may not be inherently prognostic.[25]

Several key areas of heterogeneity were identified between trials included in the NMA including sex distribution and proportion of Asian patients. These differences may result in uncertainty in the estimates of treatment effect and therefore as described in Section B.2.9.4 above, a meta-regression was performed to adjust the baseline characteristics of included studies. The majority of baseline characteristics were not identified as significant suggesting the impact of any between-trial heterogeneity on the model results would be minimal.

The NMAs utilised for OS and PFS are dependent on the proportional hazards assumption. An assessment of proportional hazards identified evidence that this assumption may not have held in three studies informing the PFS network (CheckMate 057, REVEL, and ECOG-ACRIN 1512) and two studies informing the OS network (CheckMate 057, and ECOG-ACRIN 1512). Nevertheless, for the majority of included studies, there was no clear violation of proportional hazards, and it was therefore deemed appropriate to synthesise HRs, assuming constant hazards.

In order to minimise potential biases the analysis used methods recommended by NICE TSD17 and the most robust statistical techniques for ITCs.[97, 98] An extensive SLR of published and

unpublished trials was conducted, excluding studies with methodological issues. This was followed by a thorough feasibility assessment to evaluate whether the studies included in the NMA are comparable in terms of treatment, disease, and relevant covariates. Furthermore, given the use of informative priors across models used in the ITC, the impact of the limited inconsistency identified in the assessment of inconsistency on NMA results is considered to be low (see Section B.2.9.5).

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

B.2.9.7 NMA conclusions

Overall, the results of the NMAs suggested that selpercatinib is likely to provide significant improvements in OS, PFS and ORR compared to both nintedanib plus docetaxel chemotherapy and docetaxel monotherapy in *RET* fusion-positive patients with advanced NSCLC.

B.2.10 *Adverse reactions*

Summary of LIBRETTO-001 safety analysis

- The safety of selpercatinib was assessed in two trial populations: all patients enrolled in LIBRETTO-001 regardless of tumour type or treatment history (overall safety analysis set [OSAS]), and patients with documented *RET* fusion-positive NSCLC (safety analysis set [SAS])
- Dose reductions were required in [redacted] of the OSAS and [redacted] of the IAS populations, with the most common reason being AEs: [redacted]837[redacted] and [redacted]247[redacted] in the OSAS and IAS, respectively.
- In the OSAS, Grade 3 or 4 TEAEs were reported [redacted] patients and [redacted] patients in the *RET* fusion-positive NSCLC SAS.[80]
- 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 IAS ([redacted]% and 10.9%, respectively), 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=837) 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 13th January 2023 data cut-off date
- The NSCLC Safety Analysis Set (SAS) (N=362) 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 13th January 2023 data cut-off date
- Both safety analysis sets included all 247 treatment-exposed patients with documented *RET* fusion-positive NSCLC who are the focus of this submission

From the time the informed consent form was signed until the end of the safety follow-up period (28 ± 7 days post last dose), all AEs were recorded on the appropriate electronic case report form (eCRF).[89] 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.[89]

B.2.10.1 Treatment duration and dosage

Informed by the Phase I dose escalation stage of LIBRETTO-001, the RP2D was 160 mg BID. The range of starting doses and average time on treatment were available for the IAS trial population (Table 28). Nearly all ([redacted]247 [[redacted]%]) patients in the IAS trial population received the proposed starting dose of 160 mg BID.[85] The mean time on treatment was [redacted] months with a range between [redacted] and [redacted] months. The relative median dose intensity was similar in the Overall Safety Population ([redacted]%) and in the *RET* fusion-positive NSCLC Safety Population ([redacted]%) (Table 29).

Dose reductions were required in [redacted]837 ([redacted]) patients in the OSAS and [redacted]247 ([redacted] patients in the *RET* fusion-positive IAS, with the most common reason being AEs ([redacted] and [redacted] respectively) (Table 30).[85] Dose interruptions occurred in [redacted]837[redacted]of the OSAS and [redacted]247[redacted]of the IAS, with the most common reason being AEs ([redacted]and [redacted] respectively). There were [redacted]837[redacted] and [redacted]247[redacted]dose increases in the OSAS and IAS, respectively.[85]

Table 28: Selpercatinib dosing (IAS)

	IAS (N=247)
Starting dose, n (%)	
80 mg BID	[redacted]
160 mg BID (RP2D)	[redacted]
240 mg BID	[redacted]
Time on treatment, months	
Mean (SD)	[redacted]
Median (range)	[redacted]

Abbreviations: BID: twice daily; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; QD: once daily; *RET*: rearranged during transfection; RP2D: recommended Phase II dose; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Table 14.1.1.2.1 (Section 8.2.3).

Table 29: Selpercatinib relative dose intensity (Safety Analysis Sets)

	IAS (*RET* fusion-positive NSCLC; N=247)	OSAS (overall population; N=837)
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: IAS: integrated analysis set; NSCLC: non-small cell lung cancer; OSAS: overall safety analysis set; *RET*: rearranged during transfection; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).Table JZJA.8.33.[76]

Table 30: Selpercatinib dose modifications (Safety Analysis Sets)

	IAS (*RET* fusion-positive NSCLC; N=247)	OSAS (overall population; N=837)
Dose reduction, n (%)		
Any	[redacted]	[redacted]
For AE	[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]

Note: [a]Patients started at a lower dose during dose escalation that was subsequently increased; [b]Re-escalation after a dose reduction.
Abbreviations: AE: adverse event; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; OSAS: overall safety analysis set; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).Table JZJA.8.34.[76]

AEs were graded by the Investigator, when applicable, using the National Cancer Institute Common Terminology Criteria for Adverse Events.[99]

B.2.10.2 Treatment-emergent adverse events

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

In the OSAS, [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 31). A similar pattern was observable in the NSCLC IAS. Permanent discontinuation of selpercatinib due to AEs was infrequent ([redacted]%) in the OSAS, with no predominant pattern among the individual AEs reported. [redacted] fatal TEAE within 28 days of last dose was attributed to selpercatinib in the OSAS, and [redacted] deaths related to selpercatinib occurred in the IAS.[80]

[redacted] patients in the OSAS experienced at least 1 TEAE during treatment. The most common TEAEs, defined as occurring in 15% of patients or more, in the OSAS were: oedema ([redacted]%), diarrhoea ([redacted]%), fatigue ([redacted]%), dry mouth ([redacted]%), hypertension ([redacted]%), aspartate aminotransferase (AST) increase ([redacted]%), rash ([redacted]%), abdominal pain ([redacted]%), alanine transaminase (ALT) increase ([redacted]%), constipation ([redacted]%) and nausea ([redacted]%).[80] 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 IAS analysis sets, as presented in Table 32.[80]

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/decrease or concomitant medication.

Table 31: Summary of safety trends (Safety Analysis Sets)

	IAS (*RET* fusion-positive NSCLC; N=247)	OSAS (overall population; N=837)
Any TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Grade 3 or 4 TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
TEAE leading to treatment discontinuation, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
TE-SAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Fatal TEAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]

Abbreviations: AE: adverse event; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; OSAS: overall safety analysis set; *RET* rearranged during transfection; SAE: serious adverse event; TEAE: treatment emergent adverse event.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76]

Table 32: Common TEAEs of all grades (15% or greater in any Safety Analysis Sets)

Preferred term	Maximum severity incidence, n (%)			
	IAS (*RET* fusion-positive NSCLC; N=247)		OSAS (overall population; N=837)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Oedema	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]

Dry Mouth	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension (AESI)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Decrease appetite	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolongation (AESI)	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; OSAS: overall safety analysis set; *RET* rearranged during transfection; TEAE: treatment-emergent adverse event.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023. Table JZJA.5.18. (13th January 2023 cut-off).[76]

B.2.10.3 Grade 3–4 treatment-emergent adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in [redacted] patients (Table 33). The most common Grade 3–4 events were hypertension ([redacted]), ALT increase ([redacted]%), and AST increase ([redacted]) in the OSAS. Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, less than half ([redacted] were considered by the Investigator to be related to selpercatinib. In the IAS, [redacted] patients experienced Grade 3–4 TEAEs, irrespective of relatedness to selpercatinib (Table 33). A smaller proportion ([redacted] were considered by the Investigator to be related to selpercatinib. Common TEAEs mirrored the OSAS analysis set.[80]

Table 33: Grade 3–4 TEAE (occurring in ≥2% of patients)

Preferred term	Grade 3−4 TEAEs occurring in ≥2% of patients, n (%)			
	IAS (*RET* fusion-positive NSCLC; N=247)		OSAS (overall population; N=837)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
1 or more Grade 3–4 AEs	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Grade 3−4 TEAEs occurring in ≥2% of patients, n (%)			
	IAS (*RET* fusion-positive NSCLC; N=247)		OSAS (overall population; N=837)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
ECT QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]

Note: Grade 3–4 AEs related to selpercatinib are reported if occurring in 15% or more of the populations. Grade 3–4 AEs irrespective of their relationship are reported if occurring in 2% or more of the populations.
Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG: electrocardiogram; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; NR: not reported; OSAS: overall safety analysis set; *RET* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[76] Table JZJA.5.20 (Any) and Table JZJA.8.105. (related to selpercatinib).

B.2.10.4 Treatment emergent adverse events of special interest

Based on predictions from the *RET*-related literature, the preclinical toxicology programme and clinical experience with selpercatinib, AEs of special interest were identified for focussed analysis: ALT/AST increase, drug hypersensitivity reaction, hypertension and notable event QT prolongation. These special interest AEs are monitorable and reversible with successful dose modification strategies, which allow the majority of patients who experience these events to continue safely on therapy.[85]

ALT/AST increase

In the OSAS, the TEAE of AST increase was reported in [redacted] patients ([redacted] related to selpercatinib; [redacted] Grade 3–4; [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).[80] The majority of ALT and AST TEAEs were Grade 1 or 2.[89] 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 (ALT: [redacted]; AST: [redacted]). In addition, [redacted] patients met Hy's Law criteria of drug induced liver injury.[89]

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.[89]

In the OSAS, drug hypersensitivity was observed in a [redacted]837[redacted] of patients who had one or more AE of hypersensitivity. The median time to first onset was [redacted] weeks (range: [redacted]). Grade 3 was the worst severity AE for [redacted] patients ([redacted] and there were no Grade 4 or above hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted]837[redacted] OSAS patients.[89]

Overall, interventions through dose interruption and dose reduction were successful and, in most cases, patients were able to continue study drug treatment after dose reduction and/or interruption. Of the [redacted] OSAS patients with hypersensitivity reactions, [redacted] patients underwent dose reduction and [redacted] dose interruption. Only [redacted] of the [redacted] patients were reported to permanently discontinue selpercatinib due to a hypersensitivity reaction.[89]

Hypertension

In the OSAS, the AE of hypertension was reported in [redacted]% of patients ([redacted]% considered related to selpercatinib), with [redacted]% classified as Grade 3 and [redacted]classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension [redacted]were considered to be related to selpercatinib. A similar proportion of IAS patients experienced hypertension ([redacted]247[redacted]with [redacted]247[redacted]classified as Grade 3 and [redacted] as Grade 4.[80] Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. A minority of OSAS patients required dose interruption ([redacted]and/or reduction ([redacted]%). [redacted] discontinued therapy due to an AE of hypertension.[85]

Moreover, of the 837 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.[80]

Notable Event-QT prolongation

Any grade ECG QT prolongation was reported for [redacted]837 patients ([redacted]%), with [redacted]837 ([redacted]%) considered related to selpercatinib in the OSAS.[80] The majority of events were Grade 1 or Grade 2. [redacted] patient had an AE of QTcF prolongation that was deemed serious. QTcF prolongation was manageable by selpercatinib dose interruptions ([redacted] patients) or reductions ([redacted] patients). [redacted] patient discontinued treatment due to QT prolongation in the OSAS.[85]

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.[85]

B.2.10.5 Safety conclusions

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable toxicities across both the OSAS and IAS. These toxicities were easily reversable through dose interruption or addressed through dose reduction or concomitant medication. Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent in both the OSAS and IAS ([redacted]% and [redacted]%, respectively), 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*.[80]

B.2.11 *Ongoing studies*

The LIBRETTO-001 trial is currently ongoing and [redacted].

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 previously treated patients with advanced non-squamous *RET* fusion-positive NSCLC. The key source of efficacy and safety evidence supporting selpercatinib in this position is the LIBRETTO-001 trial. LIBRETTO-001 is a multicentre, single-arm, open-label Phase I/II study. Phase I was designed to assess the PK, safety and MTD of selpercatinib, while Phase II was designed for the 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.[85]

Data presented in this submission are from the 13th January 2023 data cut-off, which provides an additional 30.29 months and 27.6 months of follow-up for overall survival (OS) and progression-free survival (PFS) data, respectively, from the LIBRETTO-001 trial as compared to data previously presented in TA760 which resulted in the recommendation of selpercatinib in previously-treated, advanced, *RET* fusion-positive NSCLC via the CDF.[2] In addition to this longer follow-up, these data are derived from a larger patient population: by the 13th January 2023 data cut-off, there were [redacted] more patients in the IAS population compared to the IAS population presented in TA760.[2] As a result, these latest PFS and OS data are associated with considerably reduced uncertainty as compared with the data presented in TA760. Whilst associated with more certainty, the latest data are consistent with the previous data cut in showing the efficacy of selpercatinib, with median PFS for the IAS population increasing from 19.29 months (95% CI: 16.5, NE) to 26.15 months (95% CI: 19.3–35.7).[76, 100]

A high ORR was observed in previously-treated, advanced, *RET* fusion-positive NSCLC patients receiving selpercatinib during the LIBRETTO-001 trial (61.5%). These results provide tangible evidence for the anti-tumour activity of selpercatinib in advanced NSCLC. In addition, 73.0% of patients in the IAS population remaining in response at 12 months demonstrates that the anti-tumour activity of selpercatinib is durable and provides a clinically meaningful delay in disease progression that works to maintain patient QoL. Furthermore, the median PFS for the IAS

population was 26.2 months at a median follow-up of 44.6 months at the most recent data-cut off.[80] This demonstrates an increase in median PFS and certainty at the latest data cut-off compared with previous data cut-offs, as median PFS was 19.32 months with uncertain 95% confidence intervals at the 16th December 2019 data cut-off.[101] Based on results from the LIBRETTO-001 trial, it is expected that 70.6% of previously-treated advanced NSCLC patients who receive selpercatinib will remain progression free at 12 months, indicating a high level of disease control and stabilisation with selpercatinib. At a median follow-of 44.6 months, median OS was 47.6 months in the IAS population. A high OS rate of 87.9% at 12 months in the LIBRETTO-001 trial further supports a high level of disease control with selpercatinib. Similarly to the PFS results, OS results from the most recent data cut-off show a higher median survival estimate with greater certainty, as at the 16th December 201 data cut-off, median OS was not estimable, with only a lower bound of 22.3 months being estimated for the 95% confidence interval.[101] The results from the 13th January 2023 data cut-off have come from a larger patient population (n=247) than the 16th December 2019 data cut-off (n=184), with an increased duration of follow-up (11 to 41.20 months for PFS), resulting in higher and more certain survival estimates being available at the most recent data cut-off.[76, 101]

Crucially, these clinical outcomes are supported by patient reported outcomes, with [redacted]% of evaluated patients reporting a sustained improvement in their global health status via EORTC-QLQ-C30 at 13th January 2023 cut-off (Section B.2.6.5). The mean change from baseline across all EORTC-QLQ-C30 subscale scores indicated that no evaluated patients experienced a meaningful worsening in any subscale. Overall, selpercatinib can maintain patients' HRQoL for longer periods of time by stimulating high and durable responses, preventing disease progression which is associated with reduced patient HRQoL.[18]

The results of the ITC showed that treatment with selpercatinib resulted in higher odds of ORR when compared to nintedanib plus docetaxel chemotherapy (OR [95% CrI]: [redacted] [[redacted], [redacted]]) and docetaxel monotherapy (OR [95% CrI]: [redacted] [[redacted], [redacted]]), respectively. In addition, treatment with selpercatinib and had a lower hazard of progression or death (PFS) compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted] [[redacted], [redacted]]) and docetaxel monotherapy (HR [95% CrI]: [redacted] [[redacted], [redacted]]), respectively. Similarly to PFS, treatment with selpercatinib and demonstrated a lower risk of death (OS) when compared to nintedanib plus docetaxel chemotherapy (HR [95% CrI]: [redacted] [[redacted], [redacted]]) and docetaxel monotherapy (HR [95% CrI]: [redacted] [[redacted], [redacted]]), respectively.

Selpercatinib has also demonstrated a tolerable safety profile across all trial patients (regardless of tumour type). While [redacted] patients experienced a TEAE, only [redacted]% and [redacted]% of patients discontinued treatment in the OSAS and SAS populations, respectively, as a result of TEAEs caused by selpercatinib.[76] 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 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 previously treated patients with advanced (Stage IIIB and IV) *RET* fusion-positive NSCLC. The high rates of durable response of *RET* fusion-positive NSCLC tumours to selpercatinib treatment, paired with self-reported improvements in patients' quality of life, support the case for the use of

selpercatinib in previously treated patients with *RET* fusion-positive NSCLC who require systemic therapy in UK clinical practice.

Strengths and limitations of the clinical evidence base

LIBRETTO-001 is highly relevant to the decision problem in terms of patient population and the outcomes considered. The study includes previously-treated patients with confirmed advanced, *RET* fusion-positive NSCLC, which is the patient population under consideration in this submission. The molecular sequencing of tumour samples was also consistent with NHS practice, given the established use of Genomic Hubs for NGS testing, with over [redacted] of patients assessed using NGS.[102]

[redacted] based in the UK, enrolling [redacted] patients into the OSAS and [redacted] into the overall NSCLC population. However, as compared with the general lung cancer population, the high proportion of patients identified as Asian (47.8%), the higher proportion of women than men (56.7%) and the high proportion of patients that have never smoked (66.8%) is consistent with the patient profile for *RET* fusion-positive NSCLC reported in the literature,[3, 40] and is anticipated to mirror the real-world patient profile in England. *RET* alterations rarely occur in NSCLC tumours with squamous histology, which is reflected by the overwhelming majority of cases in LIBRETTO-001 and all patients in the SACT dataset being diagnosed with tumours with non-squamous histology.[4, 76] The generalisability of the LIBRETTO-001 trial to the UK was confirmed by a UK expert clinician.[6] 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.[18] Both PFS and OS are 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 previously-treated patients initiated treatment on the 160 mg BID dose which is the licensed dose for use in UK clinical practice, and dose reductions for selpercatinib are included within its Summary of Product Characteristics.[10, 11] As such, it is expected that the IAS population reflects the dosing and efficacy of selpercatinib in patients who would be seen 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 previously treated *RET* fusion-positive NSCLC. This necessitated the use of advanced ITC techniques to make comparisons to interventions relevant to the decision problem. The process of generating pseudo-comparator arms to connect selpercatinib to the NMA introduced inherent uncertainty. Several key areas of heterogeneity were identified between trials included in the NMA including, sex distribution and proportion of Asian patients (see Section B.2.9).

In summary, selpercatinib demonstrated high levels of efficacy in LIBRETTO-001, combined with a tolerable safety profile. This is likely to lead to an improvement in HRQoL and an extension of life. Moreover, an ITC analysis showed that these efficacy benefits are superior to current standard of care for *RET* fusion-positive NSCLC patients (Section B.2.9). Accordingly, selpercatinib is expected to continue to fulfil an unmet need for an efficacious and tolerable

treatment option for previously treated patients with advanced *RET* fusion-positive NSCLC as it moves from the CDF to routine commissioning.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

- A cost-effectiveness model was developed to evaluate the cost-effectiveness of selpercatinib in patients with *RET* fusion-positive advanced NSCLC that has been previously treated but has not been treated with a RET inhibitor.
- The patient population was informed by data from the integrated analysis set (IAS) of the LIBRETTO-001 trial (N=247), which is reflective of the decision problem for this submission and the license for selpercatinib.
- The model adopted a partitioned survival approach with three health states: progression free (PF), progressed disease (PD) and dead, over a lifetime horizon (25 years). The model structure aligns closely with the model accepted by the NICE Committee in NICE TA760.[2]
- Parametric survival functions were applied in order to extrapolate PFS and OS data for selpercatinib and the docetaxel monotherapy arm, which also functioned as the pseudo-control (reference) arm generated through the process (see Section B.2.9).
- In order to generate extrapolations for nintedanib plus docetaxel chemotherapy for PFS and OS, the hazard ratio (HR) generated through the network meta-analysis (NMA) was applied to the reference arm.
- TSD 14 guidance was followed to determine the most appropriate extrapolations for selpercatinib and comparators, including seeking expert clinical opinion for clinical plausibility.[6]
- Costs included in the model were drug acquisition, drug administration, monitoring, subsequent therapies, health state costs, adverse events (AEs) and end of life costs.
- The utility value for the PF health state was derived from the EORTC QLQ-C30 data collected in the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young *et al.* (2015), and the utility value for the PD health state was aligned with the Committee preference in TA760.[103]

Base case cost-effectiveness results

- A severity modifier of 1.7x on the quality-adjusted life year (QALY) has been considered when evaluating the cost-effectiveness of selpercatinib in previously-treated *RET* fusion positive advanced NSCLC.
- Including the existing PAS, selpercatinib was associated with base case probabilistic ICERs of £36,831 per QALY gained versus docetaxel monotherapy and £32,836 per QALY gained versus nintedanib with docetaxel. These results were in close alignment with the base case deterministic ICERs of £37,501 and £35,105, respectively, indicating that the model is robust to parameter uncertainty.
- The results show that selpercatinib is associated with considerable QALY gains via improving PFS and OS: the incremental QALYs for patients receiving selpercatinib are estimated to be [redacted] and [redacted] versus docetaxel monotherapy and versus nintedanib with docetaxel chemotherapy, respectively (1.7x modifier).

Sensitivity and scenario analyses

- The results of the deterministic sensitivity analyses showed that only a small number of inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons, illustrating the robustness of the model to uncertainty.
- The results of the scenario analyses demonstrated that the base case ICERs were most sensitive to extrapolation curve choice for selpercatinib OS, with the extreme options explored producing ICERs in reasonable alignment with, or substantially lower than, the base case ICERs for both comparators.

Conclusions

- The cost-effectiveness analysis illustrates selpercatinib would continue to provide substantial

QALY benefits to patients in UK clinical practice if it were to be recommended via routine commissioning following its exit from the CDF. If selpercatinib were not recommended by NICE after exiting the CDF, there would be no targeted treatment options for patients with advanced, RET fusion-positive NSCLC who have been previously treated, thus representing a patient population with a poor prognosis and a significant unmet need.

B.3.1 *Published cost-effectiveness studies*

An economic systematic literature review (SLR) was conducted on 12th August 2019, and updated in September 2022 to identify all relevant literature published on previous economic models of second line treatments in patients with advanced and/or metastatic NSCLC, and to review appraisals and criticisms of these models by health technology assessment (HTA) agencies. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix G. In total, 93 unique studies relevant to HRQoL and healthcare resource use and costs were identified by the SLR.

B.3.2 *Economic analysis*

A *de novo* cost-effectiveness model was developed to assess the cost effectiveness of selpercatinib in previously treated adults with advanced *RET* fusion-positive NSCLC. The analysis was conducted from an NHS/Personal Social Services (PSS) perspective, and the model adopted a lifetime horizon (25 years) – see Section B.3.2.2 for further details.

B.3.2.1 Patient population

The economic analysis considered adults with previously treated *RET* fusion-positive advanced NSCLC, informed by data from the IAS population (N=247) from the LIBRETTO-001 trial. The IAS population is reflective of the decision problem defined in Section B.1.1 and the licence for selpercatinib.

B.3.2.2 Model structure

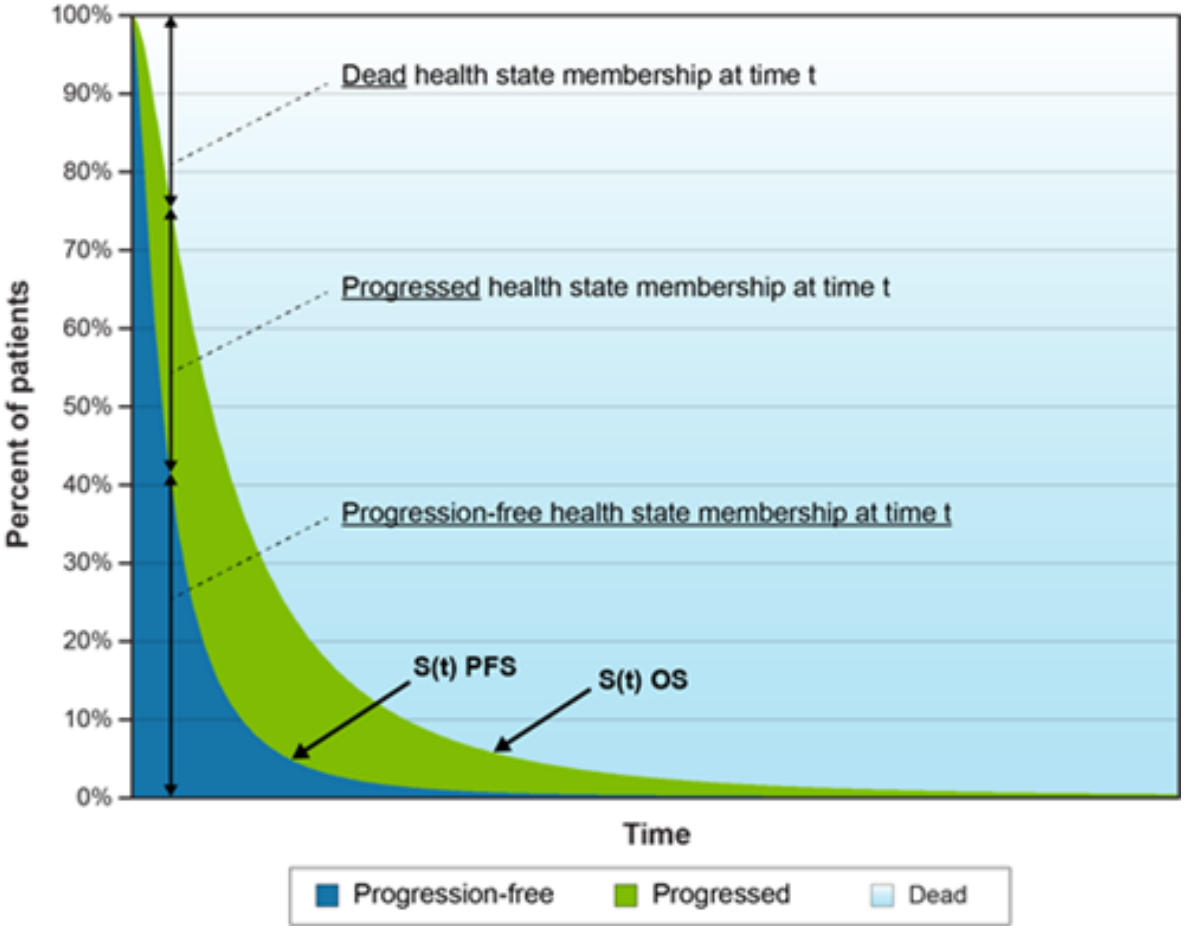
The cost-effectiveness model was constructed in Microsoft Excel and adopted a cohort-based partitioned survival model approach,[104] in line the prior NICE appraisals of RET inhibitors in NSCLC: TA760, TA812 and TA911.[1, 2, 93]

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

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

A graphical depiction of the partitioned survival model approach is presented in Figure 14 below.

Figure 14: Partitioned survival model structure



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

Adults with previously treated *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 treatment (see Section B.3.2.3). The proportion of patients in each heath state at each model cycle was then determined for each therapy from cumulative survival probabilities from PFS and OS parametric survival functions, as follows:

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

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

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

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

Features of the cost-effectiveness analysis

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

In line with the NICE reference case,[105] the analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). A lifetime time horizon of 25 years was chosen. This is similar to values chosen in recent NICE appraisals,[1, 2, 106, 107] and was deemed reasonable based on the mean baseline age of patients in LIBRETTO-001 (59.1 years) and the average life expectancy of advanced NSCLC patients. A 1-week cycle length was considered in the base case as this was deemed sufficiently granular to capture the dosing schedules of the treatments included in the model. Due to the short cycle length, it was not deemed necessary to include a half-cycle correction. Costs and effects were discounted at 3.5% annually.[105] The economic analysis is conducted using recent estimates of resource use and treatment costs available from published sources, including NHS reference costs for 2021–2022, electronic market information tool (eMIT), Personal Social Services Research Unit 2022 and the British National Formulary 2023.[108-110]

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

- TA760: selpercatinib for previously treated RET fusion-positive advanced NSCLC[2]
- TA812: pralsetinib monotherapy for RET fusion-positive advanced non-small-cell lung cancer[93]
- TA911: selpercatinib for untreated RET fusion-positive advanced NSCLC[1]

A summary of the key features of these three appraisals and justification for the design of the cost-effectiveness analysis for selpercatinib in previously treated patients with advanced *RET* fusion-positive NSCLC is provided in Table 34. The model presented in this submission has been aligned to the Committee-preferred assumptions in TA760,[2] except for approaches relating to long-term extrapolation of data (see Section B.3.3). This is because the latest data cut-off from the LIBRETTO-001 trial provides data from a larger patient population with longer follow-up, so these more mature PFS, OS and TTD data are used to inform the model in this submission. [2]

Table 34: Features of the economic analysis

Factor	Previous models of RET inhibitors in advanced NSCLC			Current appraisal	
	TA760[2]	TA812[93]	TA911[1]	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 (25 years)	Lifetime horizon (25 years)	Lifetime horizon (25 years)	Lifetime horizon (25 years)	A lifetime time horizon captures all costs and QALYs associated with selpercatinib and comparators, and is in line with the NICE reference case.
Cycle length	1 week	1 month	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	No	Yes	No	No	Due to the short length of the cycle it was not deemed necessary to include a half-cycle correction.
Treatment waning effect?	No	No	No	No	PFS and OS parametric survival curve selections for selpercatinib and comparators were validated by UK clinical expert opinion on the most clinically plausible long-term efficacy estimates.
Source of utilities	***Pre-treated*** PF: 0.713 PD: 0.628 (preferred values by the Committee)[111]	***Untreated*** TA654[112] preferred values by the Committee PF: 0.794 PD: 0.678 ***Pre-treated*** TA713[70] preferred values by the Committee	PF: 0.801 PD: 0.749	PF: 0.713 PD: 0.628	The HSUVs for progression-free and progressed disease were aligned with the Committee-preferred values in the prior NICE appraisal of selpercatinib in this indication (TA760).[2]

		PF: 0.713 PD: 0.628			
Source of costs	• NHS Reference Costs • PSSRU • Drug acquisition	• NHS Reference Costs • PSSRU • BNF • eMIT	• NHS Reference Costs • PSSRU • BNF • eMIT	• NHS Reference Costs • PSSRU • BNF • eMIT	Established sources of costs within the NHS. In line with the NICE reference case. A proportional cost associated with the detection of *RET* fusion-positive patients was included in the model for prior (pre-treated) evaluation for selpercatinib (TA760)[2], due to the implementation of national genomic testing provided by the NHS. However, this approach may underestimate the cost-efafectiveness of selpercatinib in this indication given the ongoing establishment of Genomic Hubs, as described in Section B.1.3.2, which would make *RET*-fusion testing, along with testing for other genetic drivers, part of routine NHS practice.[7] Accordingly, costs for *RET* fusion testing are considered to be absorbed by the healthcare system.

[a]Costs of adverse events were calculated multiplying the length of hospital stay resulting from adverse events, estimated by trial data, with hospitalisation costs.
Abbreviations: AE; adverse event; BNF: British National Formulary; eMIT: electronic market information tool; HSUV: health-state utility value; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; 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. It is advised that treatment is administered until disease progression or unacceptable toxicity.

Comparators

In line with the decision problem presented in Section B.1.1, docetaxel monotherapy and docetaxel with nintedanib were selected as model comparators. This is because the Committee in the prior NICE appraisal of selpercatinib for previously treated *RET* fusion-positive advanced NSCLC (TA760) concluded that immunotherapies, pemetrexed with carboplatin and platinum doublet chemotherapy are not relevant comparators in patients with *RET* fusion-positive non-squamous NSCLC in the second-line setting, as they would be rarely used at that point in the treatment pathway.[1] The Committee's conclusions were supported by clinical expert opinion during TA760, and subsequently by more recent clinical expert feedback received during the preparation of this submission.[2, 6]

As such, of the treatments currently recommended by NICE for 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 docetaxel monotherapy and docetaxel with nintedanib. Therefore, these treatments represent the only relevant comparators in this indication.

Details of interventions included in the model are summarised in Table 35.

Table 35: 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)[2, 10, 11]
Docetaxel	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 (TA347 ERG report, and confirmed via clinical expert opinion provided in March 2024)	IV docetaxel	TA347;[5] clinical expert opinion.[6]
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 (TA347 ERG report, and confirmed via clinical expert opinion provided in March 2024)	Oral nintedanib; IV docetaxel	TA347;[5] clinical expert opinion.[6]

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*

Real-world data for the treatment of patients with advanced, *RET* fusion-positive NSCLC with selpercatinib are available via the systemic anti-cancer therapy (SACT) dataset (N=[redacted]), collected from all NHS England providers during the period in which selpercatinib has been available via the CDF for previously-treated patients with *RET* fusion-positive advanced NSCLC.[4] However, as selpercatinib has been available via the CDF in this indication only since 2022, these data are currently not sufficiently mature to inform this submission. In addition to this short follow-up, the majority of patients are still on treatment – at the latest DCO, only [redacted]% (n=[redacted]) patients were identified as no longer being on treatment. As such, the pivotal clinical trial, LIBRETTO-001, provides the data that inform the cost-effectiveness analysis presented in this submission.[76]

B.3.3.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 36.These inputs were based on the baseline characteristics of patients from the IAS population (patients with previously treated NSCLC) who received selpercatinib in the LIBRETTO-001 trial. Clinical expert opinion indicated that the baseline characteristics of patients in the IAS population of the LIBRETTO-001 trial are expected to produce efficacy and safety results that are generalisable to patients in the UK, with no concerns raised regarding the representative nature of the characteristics used to inform the economic model.[6]

Table 36: Baseline characteristics for the model population

Model parameter	Value (SE)	Source
Mean age, years	59.1[redacted]	LIBRETTO-001 (IAS)
Female, %	56.7[redacted]	
Mean weight, kg	[redacted]	

Abbreviations: IAS: Integrated Analysis Set; SE: standard error.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[89]

B.3.3.2 Survival inputs and assumptions

As described in Section B.3.2.2, the model is a cohort-based PSM consisting of three mutually exclusive health states: PF, PD, and death. The proportion of patients in each health state at each weekly model cycle was determined for each therapy directly from cumulative survival probabilities from PFS and OS curves. As the follow-up periods for the relevant studies (LIBRETTO-001 and REVEL) were shorter than the model time horizon of 25 years, extrapolation from the observed OS and PFS data was required.[76, 94]

As discussed in Section B.2.9, it was necessary to generate a pseudo-control arm using IPD from the docetaxel chemotherapy plus placebo arm of the REVEL trial in order to connect selpercatinib to the NMA.[94] This pseudo-control arm was subsequently used as a reference in the survival analysis for the cost-effectiveness model to generate PFS and OS extrapolations for nintedanib plus docetaxel chemotherapy, permitting relative efficacy versus both comparators relevant to the decision problem to be evaluated. To minimise uncertainty in this process, the pseudo-control arm was adjusted for prognostic factors through the use of propensity score matching, thus accounting for key differences in characteristics between the LIBRETTO-001 trial population (informing the selpercatinib arm) and the REVEL trial population (informing the

docetaxel monotherapy arm), thereby generating a reliable treatment effect estimate for the two treatments.

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 chemotherapy plus placebo arm) through the application of parametric survival functions. PFS and OS functions for nintedanib plus docetaxel chemotherapy were then constructed through the application of a HR, as generated through the NMA described in Section B.2.9, to the reference arm extrapolation. The HR (95% credible interval [CrI]) applied to the reference arm extrapolation was [redacted] ([redacted] and [redacted] ([redacted]) for PFS and OS, respectively. Similarly, to inform long-term estimates of TTD in the model for selpercatinib, it was necessary to extrapolate the observed TTD data generated in the LIBRETTO-001 trial through the application of parametric survival functions. This was conducted to estimate duration of treatment for selpercatinib in the model. Treatment duration of docetaxel monotherapy and nintedanib with docetaxel chemotherapy were limited in the economic model to four treatment cycles and six treatment cycles, respectively, as per the maximum number of cycles where specified in the SmPC and clinical expert opinion on the typical duration of these treatments in clinical practice.[6]

The methods for survival analysis to identify the most appropriate parametric survival functions to extrapolate the selpercatinib and the reference arm followed the recommendations of NICE Decision Support Unit (DSU) TSD 14. A range of standard parametric distributions (e.g. exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) and flexible models (i.e. spline models) were explored for extrapolation.[113] For the spline models, these were developed based on the algorithm by Royston and Parmar *et al.* (2002).[114] Stratified and unstratified one-, two-, three-knot Weibull spline models were explored using the FlexSurv package in R. The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criteria [BIC]) were then estimated for each parametric function.

In determining the choice of survival model for the base case, consideration was given to the following, as per the recommendations provided in NICE DSU TSD14:[113]

- The statistical fit of the models to the trial data, based on AIC and BIC goodness-of-fit statistics. Tests for the PH assumption between treatment arms were conducted to determine the most appropriate models for consideration
- Goodness of fit of the models to the trial data was also assessed based on visual inspection against the observed KM curves
- Clinical plausibility for both short-term and long-term estimates of survival was assessed, based on feedback from UK clinical experts and published information from TA760 for selpercatinib.[2, 6] In particular, recent feedback received from a UK clinical expert on the clinical plausibility of extrapolations was considered to ensure appropriate selection for all clinical parameters.[6]

Adjustments were made in the model traces to ensure that logical inconsistencies, such as the proportion of patients alive being less than the proportion of patients alive and progression-free, could not occur (i.e. PFS was bound by OS as a minimum).

B.3.3.3 Progression free survival

As described in Section B.3.3.2, a range of stratified and unstratified parametric functions were fitted to the selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy arms. The model fit statistics (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) for these parametric survival functions are presented in Table 37. Visual assessment of the parametric survival functions to the Kaplan-Meier data for selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy was assessed through the extrapolations presented in Figure 15, Figure 16 and Figure 17, respectively.

As part of the clinical validation interviews conducted to support this appraisal, the plausibility of the long-term estimates of PFS for selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy in previously-treated *RET* fusion-positive NSCLC were discussed with a UK clinical expert in NSCLC.[6] The median and landmark estimates for the available extrapolations are presented in Table 38, Table 39 and Table 40.

Table 37: Model fit statistics for PFS parametric survival functions for selpercatinib, docetaxel monotherapy and nintedanib plus docetaxel chemotherapy arms

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[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 generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=3	[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 15: Selpercatinib PFS parametric survival function extrapolations

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

Table 38: Median and landmark rate estimates of PFS for selpercatinib in *RET* fusion-positive NSCLC

Parametric curve	Median PFS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

Figure 16: Docetaxel chemotherapy plus placebo PFS parametric survival function extrapolations

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

Table 39: Median and landmark rate estimates of PFS for docetaxel chemotherapy plus placebo in *RET* fusion-positive NSCLC

Parametric curve	Median PFS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

Figure 17: Nintedanib plus docetaxel chemotherapy PFS parametric survival function extrapolations

Abbreviations: PFS: progression-free survival.; Prop.: proportion.

Table 40: Median and landmark rate estimates of PFS for nintedanib plus docetaxel chemotherapy in *RET* fusion-positive NSCLC

Parametric curve	Median PFS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; PFS: progression-free survival; RET: rearranged during transfection.

The spline knot 1 and spline knot 3 show the best statistical fit based on AIC/BIC criteria, although the statistical fit was relatively similar across all curve choices. A UK clinical expert interviewed to support this submission estimated that between [redacted]% of patients receiving selpercatinib being progression-free 20 years after treatment initiation would be clinically plausible.[6] The clinician further identified the loglogistic curve as the most clinically plausible option, resulting in [redacted]% of patients being progression-free at 20 years. The loglogistic extrapolation also resulted in a median PFS value that aligned most closely with observed data from LIBRETTO-001 (median PFS of [redacted] months modelled by the loglogistic curve versus 26.15 months in the LIBRETTO-001 trial).[76] Therefore, based on clinician feedback, the close alignment with the LIBRETTO-001 trial data and the similar statistical fit across curve choices, the loglogistic extrapolation was selected to model PFS for selpercatinib in the base case.[6]

The clinician further considered that the landmark survival estimates resulting from the spline knot 3 curve were the most clinically plausible for both comparators, and thus this curve was selected for both comparators in the base case.[6]

Scenario analyses

In order to assess the impact of selpercatinib curve choice on the cost-effectiveness results, scenario analyses were performed in which the PFS curves associated with the highest (stratified Gompertz) and lowest (Weibull) PFS estimates at 20 years for treatment with selpercatinib were explored. The results of these scenarios are presented in Section B.3.11.3. Scenarios implementing alternative curves for the comparators were not explored given the expected limited impact of this choice on overall results.

B.3.3.4 Overall survival

A range of stratified and unstratified parametric functions were fitted to the selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy arms. The model fit statistics (AIC and BIC) for these parametric survival functions are presented in Table 41. Visual assessment of the parametric survival functions to the Kaplan-Meier data for selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy arms was assessed through the extrapolations presented in Figure 18, Figure 19 and Figure 20, respectively.

As part of the clinical validation interviews conducted to support this appraisal, the plausibility of the long-term estimates of OS for selpercatinib, docetaxel plus placebo and nintedanib plus docetaxel chemotherapy in previously-treated *RET* fusion-positive NSCLC were discussed with a UK clinical expert in NSCLC.[6] The median and landmark estimates for the available extrapolations are presented in Table 42, Table 43 and Table 44.[6]

Table 41: Model fit statistics for OS parametric survival functions for selpercatinib, docetaxel monotherapy and nintedanib plus docetaxel chemotherapy arms

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[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 generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=1	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=2	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline/Knot=3	[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; OS: overall survival.

Figure 18: Selpercatinib OS parametric survival function extrapolations

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

Table 42: Median and landmark rate estimates of OS for selpercatinib in *RET* fusion-positive NSCLC

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; OS: overall survival; RET: rearranged during transfection.

Figure 19: Docetaxel chemotherapy plus placebo OS parametric survival function extrapolations

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

Table 43: Median and landmark rate estimates of OS for docetaxel chemotherapy plus placebo in *RET* fusion-positive NSCLC

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; OS: overall survival; RET: rearranged during transfection.

Figure 20: Nintedanib plus docetaxel chemotherapy OS parametric survival function extrapolations

Abbreviations: OS: overall survival.

Table 44: Median and landmark rate estimates of OS for nintedanib plus docetaxel chemotherapy in *RET* fusion-positive NSCLC

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; OS: overall survival; RET: rearranged during transfection.

Based on AIC/BIC criteria, the exponential and loglogistic distributions show the best statistical fit. Given that the survival data presented are relatively mature at the time of the latest DCO of LIBRETTO-001 (13th January 2023), statistical fit was considered to represent an important factor in curve selection.

During interviews to support this appraisal, clinical expert opinion was elicited on which extrapolation distributions were associated with the most clinically plausible landmark survival estimates.[6] In line with its strong statistical fit, the clinician identified the exponential extrapolation as the most appropriate selection to model OS for selpercatinib and both comparators.[6] As such, the exponential curve was selected to model OS for all three treatments in the base case.

Scenario analyses

In order to assess the impact of selpercatinib curve choice on the cost-effectiveness results, scenario analyses were performed in which the OS curves associated with the highest (stratified lognormal) and lowest (stratified Weibull) OS estimates at 20 years for treatment with selpercatinib were explored. The results of these scenarios are presented in Section B.3.11.3. Scenarios implementing alternative curves for the comparators were not explored given the expected limited impact of this choice on overall results.

B.3.3.5 Time to treatment discontinuation

The model fit statistics (AIC and BIC) for the parametric survival functions explored for TTD for selpercatinib are presented in Table 45, and visual assessment of the parametric survival functions to the Kaplan-Meier data for selpercatinib was assessed through the extrapolations presented in Figure 21. The median and landmark rate estimates are presented in Table 46.

Table 45: Model fit statistics for TTD parametric survival functions for selpercatinib

Function	TTD			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[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]

Footnotes: AIC and BIC statistics represent reflect the model fit to both arms.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation.

Figure 21: Selpercatinib TTD parametric survival function extrapolations

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

Table 46: Median and landmark rate estimates of TTD for selpercatinib in *RET* fusion-positive NSCLC

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Knot 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell; NA: not applicable; RET: rearranged during transfection; TTD.

Based on AIC/BIC criteria, the generalised gamma and spline knot 1distributions showed the best statistical fit. Given that the TTD data presented are relatively mature at the time of the latest DCO of LIBRETTO-001 (13th January 2023), statistical fit was considered to represent an important factor in curve selection. In line with this, the interviewed UK clinical expert identified the generalised gamma extrapolation as the most clinically appropriate curve selection.[6] As such, the generalised gamma curve was selected to model TTD for selpercatinib in the base case.

In further alignment with UK clinical expert input, it was assumed for both comparators that patients receive the maximum length of treatment expected in clinical practice: 4 treatment cycles (12 weeks) for docetaxel and 6 treatment cycles (18 weeks) for docetaxel with nintedanib (docetaxel only given for 4 treatment cycles).[6]

Scenario analyses

Recent feedback from an expert oncologist was that patients receiving selpercatinib may be treated post-progression for a variety of clinical reasons, and that TTD may therefore be expected to be equivalent to PFS plus approximately 3 months.[6] Based on this, a scenario analysis was conducted in which time on treatment for selpercatinib was modelled using PFS data from the LIBRETTO-001 trial plus 14 weeks. For completeness, a conservative scenario in which TTD is modelled to be equal to PFS is also presented.

The results of these scenario analyses are presented in Section B.3.11.3.

B.3.3.6 Summary of survival approaches

An overview of the approaches adopted to model PFS, OS and TTD for each treatment arm in the base case cost-effectiveness analyses are presented in Table 47.

Table 47: Summary of selected base case survival approaches

Endpoint	Selpercatinib	Docetaxel monotherapy	Nintedanib plus docetaxel
PFS	Loglogistic	Spline knot 3	Spline knot 3

Endpoint	Selpercatinib	Docetaxel monotherapy	Nintedanib plus docetaxel
OS	Exponential	Exponential	Exponential
TTD	Generalised gamma	12 weeks (4 treatment cycles)	18 weeks (6 treatment cycles)

Abbreviations: NA: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

B.3.3.7 Adverse events

Probabilities of individual adverse events for each intervention were based on trial data from the IAS of the LIBRETTO-001 trial (N=247) for selpercatinib, from the total population of the REVEL trial (N=618) for docetaxel, and from the LUME-Lung 1 trial (N=652) for nintedanib plus docetaxel. Grade 3–4 adverse events with at least 2% difference in frequency between interventions were included (Table 48). Utility decrements (if any) and costs associated with each adverse event were included in the model, see Section B.3.4.4 and B.3.5.3, respectively.

Table 48: Incidence of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model

Adverse Event	Selpercatinib	Nintedanib plus docetaxel chemotherapy	Docetaxel monotherapy
Diarrhoea	[redacted]	6.60%	4.63%
Hypertension	[redacted]	0.00%	5.58%
ECG QT prolonged	[redacted]	0.00%	0.00%
Drug hypersensitivity	[redacted]	0.00%	0.00%
Haemorrhage	[redacted]	0.15%	2.39%
Fatigue	[redacted]	5.67%	14.04%
Decreased appetite	[redacted]	1.38%	2.23%
Syncope	[redacted]	0.00%	0.00%
Asthenia	[redacted]	2.30%	0.00%
Hypophosphataemia	[redacted]	0.00%	0.00%
Dyspnoea	[redacted]	4.91%	3.83%
Alanine aminotransferase increased	[redacted]	7.82%	0.00%
Aspartate aminotransferase increased	[redacted]	3.37%	0.00%
Hyponatraemia	[redacted]	2.15%	0.00%
Lymphopenia	[redacted]	0.00%	0.00%
Pneumonia	[redacted]	3.07%	0.00%
Hypokalaemia	[redacted]	0.00%	0.00%
Thrombocytopenia	[redacted]	0.00%	2.87%
Neutropenia	[redacted]	12.12%	48.80%
Anaemia	[redacted]	1.07%	2.87%
Pleural effusion	[redacted]	1.23%	0.00%

Adverse Event	Selpercatinib	Nintedanib plus docetaxel chemotherapy	Docetaxel monotherapy
Febrile neutropenia	[redacted]	7.06%	15.95%
Urinary tract infection	[redacted]	0.15%	0.00%
Decreased neutrophil count	[redacted]	32.06%	0.00%
Decreased white blood cell count	[redacted]	16.41%	0.00%
Sepsis	[redacted]	0.00%	0.00%
Leucopenia (Leukopenia)	[redacted]	2.91%	13.72%
Stomatitis	[redacted]	0.15%	4.31%
Neuropathy	[redacted]	0.00%	2.71%
Mucosal inflammation	[redacted]	0.15%	2.87%
Venous thromboembolic	[redacted]	0.15%	1.75%
General malaise	[redacted]	0.15%	0.00%
Infection	[redacted]	0.00%	0.00%
Paranychia	[redacted]	0.00%	0.00%
Malignant neoplasm progression	[redacted]	3.83%	0.00%
Pulmonary embolism	[redacted]	0.61%	0.00%
Respiratory failure	[redacted]	1.23%	0.00%
Ascites	[redacted]	0.00%	0.00%
Colitis	[redacted]	0.00%	0.00%
Acute kidney injury	[redacted]	0.00%	0.00%
Source	LIBRETTO-001	LUME-Lung 1[115]	REVEL[94]

Abbreviations: AE: adverse event; ECG: electrocardiogram; NSCLC: non–small cell lung cancer; *RET*: Rearranged during transfection.
Sources: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report (13th January 2023 cut-off);[76] LUME-Lung 1;[115] REVEL[116, 117].[94]

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 for patients with *RET* fusion-positive NSCLC treated with selpercatinib in the second-line setting, as described in Section B.2.6.5. The questionnaires were to be answered by the subject to the best of their ability, prior to receiving drug on the first day of treatment, every second cycle in the first year followed by every third cycle from cycle 13, and at the post-discontinuation follow-up visit. The same questionnaire was completed by patients who discontinued treatment due to disease progression.

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

B.3.4.2 Mapping

Given that EORTC QLQ-C30 data were collected during the LIBRETTO-001 trial, the possibility of mapping such data to the EQ-5D to capture HRQoL in patients with pre-treated *RET* fusion-positive NSCLC was explored.

Mapping techniques typically used in NSCLC models including Kontodimopulos *et al.* 2009[118] (ordinary least square regression), Marriott *et al.* 2017[119] (linear mixed regression), Rowen *et al.* 2011[120] (response mapping) and Young *et al.* 2015[103] (response mapping) were explored. The results of the different mapping algorithms are presented in Table 49 below.

Table 49: Mapping algorithms explored to convert the EORTC-QLQ-C30 data obtained from LIBRETTO-001 trial to EQ-5D-3L

Mapping technique	Mapped EQ-5D-3L values			
	PF		PD	
	Mean	SD	Mean	SD
Kontodimopoulos 2009[118]	[redacted]	[redacted]	[redacted]	[redacted]
Marriott 2017[119]	[redacted]	[redacted]	[redacted]	[redacted]
Rowen 2011[97]	[redacted]	[redacted]	[redacted]	[redacted]
Young 2015[103]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Levels; PD: progressed disease; PF: progression free; SD: standard deviation.

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

Utility values included in the model were derived from values obtained from the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young *et al.* (2015).[103] Therefore, no further extraction of HRQoL studies from the SLR to identify cost-effectiveness studies was performed.

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 Section B.1.3.1. As such, disutility values were applied to

those experiencing adverse events to estimate the reduction in HRQoL due to the event for its duration. All adverse reactions were assumed to occur in the first cycle of the model and last for a specified duration. This approach is consistent with the Committee-accepted approach in the cost-effectiveness analysis presented in TA760.[2]

In further alignment with the accepted approach in TA760, utility decrements for adverse events and their associated duration were based on values from previous NICE technology appraisals.[2] The decrements, duration and QALY losses for each adverse event as applied in the model are presented in Table 50.

Table 50: Adverse event disutility decrements applied in the cost-effectiveness model

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	0.000	0.0	0.0000	Decrement: 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	0.000	14.7	−0.0020	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	0.000	0.0	0.0000	Decrement: Assumption
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	0.000	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	0.000	0.0	0.0000	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; Duration: Assumption
Neuropathy	−0.0850	15.0	−0.0035	Decrement: NICE TA428; Duration: Assumption

Abbreviations: ECG: electrocardiogram; QALY: quality-adjusted life year; NICE: National Institute for Health and Care Excellence.
Source: KEYNOTE-010 (TA428);[121] NICE TA428;[69] NICE TA476;[122]; NICE TA484;[111]

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

Health state utility values (HSUVs) were applied to the progression-free and progressed health states to estimate HRQoL. These values for the progression-free and progressed disease health states were aligned with the Committee preference estimates in TA760 and are presented in Table 51.[2] The PF HSUV was derived in TA760 as the mid-point between the company-submitted base case value (derived from values obtained from the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young *et al.* 2015) and the EAG-preferred value (sourced from a prior second-line NSCLC appraisal of nivolumab, TA713.[2, 70, 103]

Table 51: Summary of utility values used in the base case cost-effectiveness analysis

Health state	Value	95% CI	Source/Justification
PF	0.713	0.573–0.853	Committee-preferred estimate in TA760[2]
PD	0.628	0.665–0.712	Committee-preferred estimate in TA760[2]

Abbreviations: CI: confidence interval; EAG: external assessment group; PD: progressed disease; PF: progression-free; SD: standard deviation; SE: standard error.

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

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 in the second line setting. 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.

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

- Section B.3.5.1: Drug acquisition, administration and monitoring

- Section B.3.5.1: Subsequent treatments
- Section B.3.5.2: Medical management of the condition by health state
- Section B.3.5.3: AEs
- Section B.3.5.4: End of life (terminal care) and genetic testing costs

As described in 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 National Formulary (BNF).

B.3.5.1 Intervention and comparators' costs and resource use

The drug acquisition costs for selpercatinib and comparators were extracted from the BNF or eMIT and are presented in Table 52. For selpercatinib, a PAS discount of [redacted]% has been applied in the model. Drug acquisition costs for comparators were based on their list price.

For adjusted-dose interventions a mean body weight estimate of [redacted] kg and a body surface area of [redacted] m^2 were used, sourced from the LIBRETTO-001 trial.

Table 52: Drug acquisition costs for selpercatinib and relevant comparators (docetaxel monotherapy and nintedanib plus docetaxel chemotherapy)

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)	Source
Selpercatinib (list price)					
Selpercatinib	Capsules	80 mg	112	8,736.00	BNF (2023)[110]
Selpercatinib	Capsules	40 mg	168	6,552.00	BNF (2023)[110]
Selpercatinib (PAS price)					
Selpercatinib	Capsules	80 mg	112	[redacted]	Eli Lilly (data on file)
Selpercatinib	Capsules	40 mg	168	[redacted]	Eli Lilly (data on file)
Docetaxel monotherapy					
Docetaxel	Vial	20 mg/ml	8 ml	16.04	BNF (2023)[110]
Docetaxel + nintedanib					
Docetaxel	Vial	20 mg/ml	8 ml	16.04	BNF (2023)[110]
Nintedanib	Capsules	100 mg	60, 120	2151.10	BNF (2023)[110]

Abbreviations: BNF: British National Formulary; eMIT: Electronic market information tool; PAS: Patient Access Scheme.
Source: BNF (2023),[110] eMIT (2023)[109], Eli Lilly and Company Ltd. Data on file.

The mean dose intensity observed in the LIBRETTO-001 trial ([redacted]%) was used to account for dose reductions due to toxicity control and weight-based dosing, and any treatment breaks. In the absence of these data for the comparators, conservatively, an RDI equivalent to that for selpercatinib from LIBRETTO-001 was applied. In the base case, drug wastage was assumed. For IV drugs, it is assumed that unused treatment in open vials is discarded and for oral drugs the cost of whole tablets is assumed. Drug acquisition costs are divided into treatment periods according to the dosing schedules of each treatment, as presented in Table 53. The derivation of the treatment cycle costs for selpercatinib at each dose level is provided in Table 54 to Table 56 below.

Table 53: Treatment costs included in cost effectiveness model

Treatment	Cycle length, weeks	Period 1 cost, £	Period 2 cost, £	Period 3 cost, £	Source
Selpercatinib					
Selpercatinib (160 mg twice daily, oral)[a]	4	[redacted]	[redacted]	-	Dose: Prescribing information Dose intensity: LIBRETTO-001
Docetaxel monotherapy					
Docetaxel (75 mg/m^2, every 3 weeks, IV, up to 6 cycles)	3	16.39	14.09	-	Dose: TA403 Dose intensity: Assumed same as selpercatinib
Nintedanib plus docetaxel chemotherapy					
Docetaxel (75 mg/m^2, every 3 weeks, IV, up to 4 cycles)	3	16.39	14.09	-	Dose: TA347 Dose intensity: Assumed same as selpercatinib Dose intensity: Assumed same as selpercatinib
Nintedanib (200 mg twice daily, oral)	3	[redacted]	[redacted]	[redacted]	
Total	3	[redacted]	[redacted]	[redacted]	

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+.
Abbreviations: IV: intravenous; NICE: National Institute for Health and Care Excellence.
Source : TA403,[123] TA347,[5] Eli Lilly and Company Ltd. Data on file.[76]

Table 54: 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	112	[redacted]	[redacted]	2	14	112	[redacted]
120 mg, orally, twice daily	80	112	[redacted]	[redacted]	1	14	56	[redacted]
	40	168	[redacted]	[redacted]	1	14	56	
80 mg, orally, twice daily	80	112	[redacted]	[redacted]	1	14	56	[redacted]
40 mg, orally, twice daily	40	168	[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 55: Weighted drug acquisition costs for selpercatinib in treatment cycle 1 (including dose reductions)

Dose	Patients on each dose, %	Weighted cost per treatment cycle[a] (£)
160 mg, twice daily	[redacted]	[redacted]
80 mg, twice daily	[redacted]	

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

Table 56: Weighted drug acquisition costs for selpercatinib in treatment cycles 2+ (including dose reductions)

Dose	Patients on each dose, %	Weighted cost per treatment cycle[a] (£)
160 mg, twice daily	[redacted]	[redacted]
120 mg, twice daily	[redacted]	
80 mg, twice daily	[redacted]	
40 mg, twice daily	[redacted]	

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

Administration costs

Administration costs were based on NHS Reference Costs 2021/22 and PSSRU 2022.[108, 124] For oral drugs (selpercatinib and nintedanib), 12 minutes of pharmacy time based on a Band 6 hourly wage (£11.00)[124] was assumed every 30 days (consistent with the assumption in NICE TA520).[71] Additional drug administration costs for IV drug administration were taken from relevant TAs, as summarised in Table 57.

During treatment with any of the three interventions, patients were assumed to have one oncologist visit every 3 weeks (£221.48).[71] In addition, in alignment with the SmPC, patients treated with selpercatinib received 7 ECGs.[10, 11]

The drug administration costs used in this submission are reported in Table 57.

Table 57: Drug administration and monitoring costs for selpercatinib and comparators

Parameter	Cost (£)	Source
Administration		
Selpercatinib	11.00	NICE TA520[71]; PSSRU 2022 Table 9 Band 6 hourly wage (12 minutes pharmacy time)
Docetaxel monotherapy	207.59	NICE TA520[71]; NHS 2021/22 SB12Z outpatient (60 minute IV infusion)
Docetaxel + nintedanib	218.59	NICE TA520[71]; PSSRU 2022 Table 9 Band 6 hourly wage (12 minutes pharmacy time) ; NICE TA520 ; NHS 2021/22 SB12Z outpatient (60 minute IV infusion)
Monitoring		
Oncologist visit (all interventions)	221.48	Department of Health 2021–2022, NICE TA520[71]
ECG (7 required for selpercatinib only)	222.62 per ECG	NHS Reference costs 2021/22 (Outpatient – Medical Oncology Service)

Abbreviations: ECG: electrocardiogram; NHS: National Health Services; NICE: National Institute for Health and Care Excellence; PSSRU: Personal Social Services Research Unit.

Subsequent treatments

The approach to modelling subsequent treatments is in alignment with the Committee-preferred approach in TA760.[2] The cost estimates are presented in Table 58.

The cost of subsequent treatment was assumed to be independent of survival post-progression and was applied in the model as a one-off cost at the time of disease progression. 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, sourced from a previous NICE appraisal in NSCLC (TA520), and the percentage of patients modelled to receive each treatment is based on the NICE appraisal of nintedanib with docetaxel chemotherapy in NSCLC (TA347).[5, 71] TA520 and TA347 further informed the pattern of subsequent systemic treatments for NSCLC following second line therapy, which was based on the type of treatment received, categorised as selpercatinib or chemotherapy.[5, 71] The pattern of subsequent treatments for selpercatinib is assumed to be similar to immunotherapies.

Table 58: Subsequent therapy distributions following second-line treatment

Therapy	Cost per cycle (£)	Administration costs (£)	Duration of treatment (weeks)	Mean cost per patient (£)	Patients treated with (%)	
					Selpercatinib	Chemotherapy[a]
Docetaxel	13.61	207.59	11.64	858.27	14.9	0.0
Carboplatin	15.99	256.95	13.05	1,187.33	8.7	25.0
Gemcitabine	112.56	622.78	17.48	3,213.42	7.7	7.7
Erlotinib	353.11	11.00	10.80	983.09	5.5	5.5
Pemetrexed	543.00	207.59	16.49	4,125.75	4.9	0.0
Vinorelbine	140.89	207.59	12.11	4,220.12	5.1	5.1
Radiotherapy	13.61	207.59	20.58	11,989.97	55.0	56.6

Footnotes: [a]Chemotherapy represents docetaxel either as a monotherapy or in combination with nintedanib (both relevant comparators to selpercatinib in this submission).
Sources: NICE TA520;[71] NICE TA347.[5]

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 previously validated by clinicians, and were informed by the latest NHS reference (2021/2022) and PSSRU (2022) costs.[2, 6, 71, 108, 124] These data are displayed in Table 56. The per cycle cost for the PF health state was £167.90, whilst the per cycle costs for PD was £155.04.

Table 59: Resource use per 3-week period by health state

Resource	PF	PD	Unit cost, £	Total PF, £	Total PD, £
GP surgery	0.63	1.00	52.03	32.78	52.03
GP home visit	0.00	0.25	76.49	0.00	19.12
Oncologist visit	0.80	0.46	221.48	177.18	101.88
Full blood test	1.00	1.00	2.96	2.96	2.96
Liver function test	1.00	0.46	1.55	1.55	0.71
Renal function test (with electrolytes)	1.00	0.46	1.55	1.55	0.71
CT scan (thorax or abdominal)	0.28	0.28	181.82	50.91	50.91
Palliative care days	2.00	2.00	118.39	236.78	236.78

Abbreviations: CT: Computerised tomography; GP: general practitioner; PD: progressed disease; PF: progression free.
Source: TA520;[71] NHS Reference Costs 2021/22;[108] PSSRU (2022);[124]

B.3.5.3 Adverse reaction unit costs and resource use

Mean cost per adverse event applied in the cost-effectiveness analyses are reported in Table 60. Adverse event costs were applied in the model according to the incidences presented in Section B.3.4.4.

Table 60: Costs per adverse event applied in the cost-effectiveness model

Adverse event	Mean cost, £	Source
Diarrhoea	3,436.08	NHS Reference Costs 2021/22; TA621
Hypertension	2,300.49	NHS Reference Costs 2021/22; TA516
ECG QT prolonged	1,649.11	NHS Reference Costs 2021/22; TA516
Drug hypersensitivity	1,682.77	NHS Reference Costs 2021/22; Assumption
Haemorrhage	500.00	Assumption
Fatigue	4,223.59	NHS Reference Costs 2021/22; TA621
Decreased appetite	8,262.82	NHS Reference Costs 2021/22; Assumption
Syncope	2,796.64	NHS Reference Costs 2021/22; Assumption
Asthenia	4,223.59	NHS Reference Costs 2021/22; TA621
Hypophosphataemia	3,436.08	NHS Reference Costs 2021/22; Assumption
Dyspnoea	0.00	NHS Reference Costs 2021/22; TA484
Alanine aminotransferase increased	3,514.10	NHS Reference Costs 2021/22; TA621

Aspartate aminotransferase increased	3,514.10	NHS Reference Costs 2021/22; TA621
Hyponatraemia	0.00	Assumption
Lymphopenia	6,779.22	NHS Reference Costs 2021/22; Assumption
Pneumonia	2,855.22	NHS Reference Costs 2021/22; TA520
Hypokalaemia	3,436.08	Assumption
Thrombocytopenia	3,961.40	NHS Reference Costs 2021/22; Assumption
Neutropenia	3,676.55	NHS Reference Costs 2021/22; Assumption
Anaemia	2,980.26	NHS Reference Costs 2021/22; TA520
Pleural effusion	3,916.39	NHS Reference Costs 2021/22; Assumption
Febrile neutropenia	6,186.61	TA484
Urinary tract infection	5,169.89	NHS Reference Costs 2021/22; Assumption
Decreased neutrophil count	3,676.55	NHS Reference Costs 2021/22; Assumption
Decreased white blood cell count	6,779.22	Assumed same as lymphopenia
Sepsis	2,855.22	NHS Reference Costs 2021/22; Assumption
Leucopenia (leukopenia)	6,779.22	Assumed same as lymphopenia
Stomatitis	0.00	TA428; Assumption
Neuropathy	0.00	TA428; Assumption
Mucosal inflammation	0.00	Assumed same as stomatitis
Venous thromboembolic	1,418.32	NHS Reference Costs 2021/22
General malaise	0.00	Assumption
Infection	5,169.89	NHS Reference Costs 2021/22
Paranychia	0.00	GP visit and antibiotics
Malignant neoplasm progression	0.00	Accounted for in post-progression health state
Pulmonary embolism	2,354.42	NHS Reference Costs 2021/22
Respiratory failure	3,719.73	NHS Reference Costs 2021/22
Ascites	7,642.42	NHS Reference Costs 2021/22
Colitis	3,436.08	NHS Reference Costs 2021/22
Acute kidney injury	3,734.59	NHS Reference Costs 2021/22

Abbreviations: ECG: echocardiogram; NHS: National Health Service.
Source: NHS Reference Costs 2021/22;[108] TA428;[69] TA621;[125] TA516;[126] TA484;[111] TA520[71]

B.3.5.4 Miscellaneous unit costs and resource use

End of life costs

A one-off end of life cost of £4,761.14 (Table 61) was also included based on costs included in TA520,[71] which considered hospital admission and excess bed days, Macmillan nurse home visits and hospice care stays.

Table 61: End of life unit costs in the second-line setting

	Mean	Proportion of patients	Unit cost, £
Hospital admission	1	–	4,721.27
+ excess bed days	0.84	55.8%	1,186.22

Macmillan nurse home visits	50	27.3%	42.00
Hospice care stay	1	16.9%	5,901.58

Source: TA520;[71] NHSRC;[108,] Department of Health [127] PSSRU (2022).[124]

Genetic testing costs

As described in Section B.1.3, recent establishment of Genomic Hubs has allowed testing for *RET* and other genetic mutations of tumour samples to become routine. Therefore, a proportional cost of [redacted] per tested patient provided by NHSE&I for the previous appraisals of selpercatinib in pre-treated advanced *RET* fusion-positive NSCLC (TA760)[2] and in treatment-naïve advanced *RET* fusion-positive NSCLC (TA911)[1] was applied in the base case.

B.3.6 *Severity*

The severity modifier tool developed by SCHARR and Lumanity was used to calculate the absolute and proportional severity modifiers.[128] A summary of the features of the QALY shortfall analysis is provided in Table 62. In line with the NICE reference case, the Hernandez-Alava 2017 study, which mapped the EQ-5D-5L to the 3L, was used to inform the base case economic analysis.[105, 129]

The analysis produced a proportional shortfall of 92.88 and 91.43 versus docetaxel monotherapy and nintedanib plus docetaxel chemotherapy, respectively (Table 63). As per the NICE methods manual (PMG36), this translates to a QALY modifier of 1.2 versus both comparators, although this is very close to the threshold needed for application of the 1.7x modifier.[105] It is notable that patients with previously treated NSCLC have a considerable unmet need, demonstrating a median OS of 10.1 months or 9.1 months if treated with nintedanib plus docetaxel or docetaxel monotherapy, respectively, in the LUME-Lung 1 study.[115] Furthermore, the NICE end-of-life criteria were met in the previous appraisal for selpercatinib in pre-treated *RET* fusion-positive advanced NSCLC (TA760), resulting in a willingness-to-pay threshold approximately equivalent to the application of a 1.7x QALY modifier.[2]

As such, a QALY modifier of 1.7x versus both comparators is appropriate to consider for this submission and is applied in the economic analysis results presented in Sections B.3.10 and B.3.11.

Table 62: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution (Female)	56.7	Section B.3.3.1
Starting age	59.1	

Abbreviations: PD: progressed disease; PF: progression free; QALY: quality adjusted life year.

Table 63: Summary of QALY shortfall analysis using Hernandez Alava et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018 (base case)

	Docetaxel monotherapy	Nintedanib plus docetaxel
Expected remaining QALYs for the general population	13.07	13.07
Total QALYs that people living with a condition would be expected to have with current treatment	0.93	1.12

Absolute QALY shortfall	12.14	11.95
Proportional QALY shortfall	92.88	91.43
QALY weight	**1.2**	**1.2**

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

B.3.7 *Uncertainty*

RET-fusion positive advanced NSCLC is a rare condition, occurring in approximately 1–2% of NSCLC cases (Section B.1.3.1).[3] As such, in order to generate relative efficacy estimates for selpercatinib compared to relevant comparators, data from advanced NSCLC studies where *RET* fusion-positive patients were not specifically recruited for, nor their status tested or reported, had to be included in the NMA. Whilst this may be considered to potentially result in uncertainty in the relative efficacy estimates, studies such as Hess *et al.* have confirmed that the real prognostic influence of *RET* mutations remains unclear (see Section B.1.3.1) and therefore, as specified in Section B.2.8, adjustments relating to the presence of *RET* fusion were not made to these data.[25] This assumption is in line with the accepted assumption in TA760, TA911 for selpercatinib in both the pre-treated and treatment-naïve setting, respectively.[1, 2]

B.3.8 *Managed access proposal*

N/A – following a period in the CDF, selpercatinib is positioned for routine commissioning.

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

B.3.9.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 64.

Table 64: Summary of variables applied in the economic model (base case analysis)

Variable	Input	Measurement of uncertainty: distribution	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	N/A	
Patient characteristics			
Mean age, years (SE)	59.1[redacted]	Normal	Section B.3.2.1
Female, % (SE)	56.7[redacted]	Beta	
Mean weight, kg (SE)	[redacted]	Normal	
Clinical inputs			
OS (selpercatinib)	Exponential	N/A	Section B.3.3
PFS (selpercatinib)	Loglogistic	N/A	
OS (comparators)	Exponential	N/A	
PFS (comparators)	Spline knot 3	N/A	
NMA HRs (comparators)	*Various*	N/A	Section B.3.3.2

TTD (selpercatinib)	Generalised gamma	N/A	Section B.3.3.5
Adverse events, incidence	*Various*	N/A	Section B.3.3.7
Utility inputs			
Utility for PF	0.713	Beta	Section B.3.4.5
Utility for PD	0.628	Beta	
Drug acquisition costs			
Selpercatinib price: 112 x 80 mg tablets	[redacted]	N/A	Section B.3.5.1
Selpercatinib price: 168 x 40 mg tablets	[redacted]	N/A	
Docetaxel price: 1 x 20mg/mL vial (8 mL)	£16.04	N/A	
Nintedanib price: 60, 120 x 100 mg capsules	£2,151.10	N/A	
Include drug wastage	Yes	N/A	Section B.3.5.1
Cost per treatment cycle: selpercatinib	*Various*	N/A	Section B.3.5.1
Cost per treatment cycle: comparators	*Various*	N/A	
Drug administration costs			
Selpercatinib	£11.00	Gamma	Section B.3.5.1
Docetaxel monotherapy	£207.59	Gamma	
Nintedanib + docetaxel chemotherapy	£218.59	Gamma	
Monitoring costs			
Oncologist visit	£221.48	Gamma	
ECG (selpercatinib specific)	£222.62	Gamma	
Subsequent therapy			
Selpercatinib	£7,546.59	*Varies with dose intensity, BSA/weight, and administration costs*	Section B.3.5.1
Immunotherapy	£7,546.59	*Varies with dose intensity, BSA/weight, and administration costs*	
Chemotherapy	£7,604.58	*Varies with dose intensity, BSA/weight, and administration costs*	
Health state costs			
Health state costs per cycle: PF	£167.90	Gamma	Section B.3.5.2
Health state costs per cycle: PD	£155.04	Gamma	
Other costs			
Adverse event costs	*Various*	Gamma	Section B.3.5.3
End of life costs	£4,761.14	Gamma	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.3.9.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 65.

Table 65: Modelling assumptions

Parameter (setting)	Assumption	Justification	Addressed in scenario analysis?
Long-term extrapolations	The selected parametric survival functions for selpercatinib and the comparators were deemed appropriate to represent long-term treatment outcomes	Assumptions of long-term efficacy are necessary to generate cost-effectiveness results over a lifetime horizon.	Yes; alternative parametric survival functions for selpercatinib that produced the highest or lowest estimates for PFS and OS at 20 years were explored in scenario analyses.
Modelling TTD	TTD data available from the LIBRETTO-001 trial were used to model the mean time for which patients receive selpercatinib, with the curve choice validated as the most clinically appropriate curve selection for modelling TTD in UK clinical practice.	Recent feedback from an expert oncologist was that patients receiving selpercatinib may be treated post-progression for a variety of clinical reasons, and that TTD may therefore be expected to be equivalent to PFS plus approximately 3 months.	Yes; modelling TTD using PFS plus 14 weeks and TTD using PFS were explored in a scenario analysis
Patients' baseline *RET* status	The pattern of specific *RET* alterations is representative of that in patients in routine practice or that the treatment effect is consistent across different *RET* alterations.	No data are available to evaluate whether the LIBRETTO-001 population is similar to the routine clinical practice population in terms of the pattern of specific RET alterations.	NA
Utility values	Utility weights for patients with *RET*-altered tumours are equivalent to patients with *RET* wild-type tumours.	Clinical expert opinion has previously been elicited suggesting that HRQoL in patients with *RET*-altered tumours may be expected to be similar to that of the wider patient population with the same tumour type.	NA
Cost of subsequent treatment	The cost of subsequent systemic treatment is assumed to be independent of	This is expected to be a conservative assumption as less discounting will be	NA

	survival post-progression, and is applied in the model as a 1-off cost at the time of progression. For simplicity, the timing was not adjusted in analyses where selpercatinib treatment is continued beyond disease progression.	applied for the costs of subsequent systemic treatment.	

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire; HRQoL: health-related quality of life; NA: not applicable; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; RET: rearranged during transfection; TTD: time to treatment discontinuation.

B.3.10 *Base-case results*

A summary of the base case analysis for *RET* fusion-positive NSCLC in the second line setting 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.

As discussed in Section B.3.6, a severity modifier of 1.7x on the QALY has been considered in the presented base case (Section B.3.10.1) and scenario (Section B.3.11.3) cost-effectiveness results. For completeness, the base case results at a severity modifier of 1.2x are presented in Table 68 and Table 69, with scenario analysis results presented at a severity modifier of 1.2x presented in Appendix M. The probabilistic and deterministic results, presented in Sections B.3.11.1 and B.3.11.2, respectively, are presented with no additional severity weighting (modifier of 1.0x).

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

The base case deterministic and probabilistic cost-effectiveness results for selpercatinib versus the relevant comparators for use in in the second line setting are presented in Table 66 and Table 67, 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 docetaxel monotherapy and nintedanib plus docetaxel, respectively. The total costs for patients receiving selpercatinib are estimated to be £[redacted] compared with £[redacted] and £[redacted] for patients treated with docetaxel monotherapy and nintedanib plus docetaxel, respectively.

In the probabilistic base case, this resulted in pairwise ICERs for selpercatinib of £36,831 and £32,836 per QALY gained versus nintedanib plus docetaxel and docetaxel monotherapy, respectively.

Table 66: Probabilistic base-case results (with selpercatinib PAS, 1.7x severity modifier QALY weighting)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs (1.7x modifier)	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	Fully Incremental ICER (£/QALY)
Docetaxel monotherapy	1.424	[redacted]	[redacted]	3.645	[redacted]	[redacted]	36,831	[redacted]
Nintedanib + docetaxel chemotherapy	1.695	[redacted]	[redacted]	3.374	[redacted]	[redacted]	32,836	[redacted]
Selpercatinib	5.069	[redacted]	[redacted]	-	[redacted]	[redacted]	-	36,831

[a] At a £30,000/QALY willingness-to-pay threshold.
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

Table 67: Deterministic base-case results (with selpercatinib PAS, 1.7x severity modifier QALY weighting)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs (1.7x modifier)	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	Fully Incremental ICER (£/QALY)
Docetaxel monotherapy	1.423	[redacted]	[redacted]	3.645	[redacted]	[redacted]	37,501	-
Nintedanib + docetaxel chemotherapy	1.699	[redacted]	[redacted]	3.370	[redacted]	[redacted]	35,105	Extendedly dominated
Selpercatinib	5.068	[redacted]	[redacted]	-	[redacted]	[redacted]	-	37,501

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

Table 68: Probabilistic base-case results (with selpercatinib PAS, 1.2x severity modifier QALY weighting)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs (1.2x modifier)	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	Fully Incremental ICER (£/QALY)
Docetaxel monotherapy	1.424	[redacted]	[redacted]	3.645	[redacted]	[redacted]	52,177	[redacted]
Nintedanib + docetaxel chemotherapy	1.695	[redacted]	[redacted]	3.374	[redacted]	[redacted]	46,518	[redacted]
Selpercatinib	5.069	[redacted]	[redacted]	-	[redacted]	[redacted]	-	52,177

[a] At a £30,000/QALY willingness-to-pay threshold.
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

Table 69: Deterministic base-case results (with selpercatinib PAS, 1.2x severity modifier QALY weighting)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs (1.2x modifier)	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	Fully Incremental ICER (£/QALY)
Docetaxel monotherapy	1.423	[redacted]	[redacted]	3.645	[redacted]	[redacted]	53,126	-
Nintedanib + docetaxel chemotherapy	1.699	[redacted]	[redacted]	3.370	[redacted]	[redacted]	49,732	Extendedly dominated
Selpercatinib	5.068	[redacted]	[redacted]	-	[redacted]	[redacted]	-	53,126

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

B.3.11 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.11.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.11.1 Probabilistic sensitivity analysis

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

The probabilistic cost-effectiveness planes for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel chemotherapy are presented in Figure 22 and Figure 23, respectively.

The cost-effectiveness acceptability curves for selpercatinib versus docetaxel monotherapy and versus nintedanib plus docetaxel chemotherapy are presented in Figure 24 and Figure 25, respectively.

Figure 22: Probabilistic cost-effectiveness plane for selpercatinib vs docetaxel monotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

Abbreviations: QALY: quality-adjusted life year.

Figure 23: Probabilistic cost-effectiveness plane for selpercatinib vs nintedanib plus docetaxel chemotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

Abbreviations: QALY: quality-adjusted life year.

Figure 24: Cost-effectiveness acceptability curve for selpercatinib vs docetaxel monotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 25: Cost-effectiveness acceptability curve for selpercatinib vs docetaxel plus nintedanib chemotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year.

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for selpercatinib versus docetaxel monotherapy and nintedanib plus docetaxel chemotherapy are presented in Figure 26 and Figure 27, respectively. The top 25 most influential parameters on the base case are presented in each case.

A small number of inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons and both treatment lines. For both comparators, the inputs that had the greatest impact on the ICER were the PF HSUV for selpercatinib and the discount rate for costs and outcomes. Discount rate for costs and effects used in the model aligned with NICE reference case (3.5%).

Figure 26: DSA tornado diagram for selpercatinib vs docetaxel monotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

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

Figure 27: DSA tornado diagram for selpercatinib vs nintedanib plus docetaxel chemotherapy (with selpercatinib PAS, 1.0x severity modifier QALY weighting)

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

B.3.11.3 Scenario analysis

Several scenario analyses were conducted probabilistically to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model. A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table 70. Scenario analysis results using a 1.2x severity modifier QALY weighting are included in Appendix M.

The results of the scenario analyses demonstrated that the base case ICERs were most sensitive to extrapolation curve choice for selpercatinib OS, with the extreme options explored producing ICERs in reasonable alignment with, or substantially lower than, the base case ICERs for both comparators.

Table 70: Scenario analysis results for selpercatinib versus relevant comparators (with selpercatinib PAS, 1.7x severity modifier QALY weighting)

Scenario		Selpercatinib vs docetaxel monotherapy			Selpercatinib vs nintedanib + docetaxel chemotherapy		
		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	***36,831***	[redacted]	[redacted]	***32,836***
1	Selpercatinib PFS = Stratified Gompertz	[redacted]	[redacted]	36,614	[redacted]	[redacted]	32,695
2	Selpercatinib PFS = Weibull	[redacted]	[redacted]	36,960	[redacted]	[redacted]	32,687
3	Selpercatinib OS = Stratified Lognormal	[redacted]	[redacted]	29,951	[redacted]	[redacted]	26,599
4	Selpercatinib OS = Stratified Weibull)	[redacted]	[redacted]	38,157	[redacted]	[redacted]	33,675
5	Selpercatinib TTD = PFS + 14 weeks	[redacted]	[redacted]	36,132	[redacted]	[redacted]	31,923
6	Selpercatinib TTD = PFS	[redacted]	[redacted]	34,574	[redacted]	[redacted]	30,376

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

B.3.11.4 Summary of results of sensitivity analyses

The probabilistic and deterministic base case results were in close alignment, indicating that the model is robust to parameter uncertainty. Similarly, the DSA results identified a small number of key influential parameters including the PF HSUV for selpercatinib and the discount rate for costs and outcomes, but overall the model largely showed robustness to uncertainty in the majority of parameters. Scenario analyses conducted to address sources of uncertainty in the model demonstrated that there was limited variation in the ICER.

B.3.12 *Subgroup analysis*

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

B.3.13 *Benefits not captured in the QALY calculation*

If recommended, selpercatinib will continue to be the only *RET* receptor kinase inhibitor available for previously treated *RET*-fusion positive advanced NSCLC patients in the UK. Currently, these patients receive the same treatments as those without recognised oncogenic markers. Prognosis in these patients is poor; people diagnosed with advanced NSCLC have a significantly reduced chance of survival: around 57% of people diagnosed at the early stages of disease will survive for five years or longer, whilst only 3% of those diagnosed with advanced disease will survive as long.[130] Indeed, in the LUME-Lung 1 study, patients with previously treated NSCLC had a median OS of 10.1 months if treated with nintedanib plus docetaxel versus 9.1 months if treated with docetaxel monotherapy.[115] On top of physical disease symptoms, people with this condition experience anxiety and depression due to the impact of diagnosis, conversation around the disease, impact of treatment and predicted course of the disease.[41] The availability of a treatment that is specifically targeted to the oncogenic driver of their condition may offer hope to patients and their families of delayed disease progression and improved survival. This is not captured in the QALY calculations.

In addition, owing to its targeted mechanism of action, selpercatinib is associated with a tolerable safety profile, unlike current clinical management, which is often associated with off-target side effects. A recent survey conducted by Yong *et al.* (2021) investigating treatment preferences in advanced NSCLC of 308 patients and 188 caregivers, found patients valued treatments which were not associated with AEs that may lead to hospitalisation.[131] This patient preference for a treatment with an improved safety profile is not captured in the QALY calculations.

A final notable benefit of selpercatinib is that it has a convenient oral method of administration. Current alternatives to selpercatinib in UK clinical practice require intravenous infusion (at least in part), and therefore need to be administered in a specialised infusion clinic, resulting in a greater economic burden on NHS resources. In addition, a review of the scientific literature reporting on patient preferences (including lung cancer patients) for oral compared to IV administration of cancer treatments by Eek *et al*. (2016) found the majority (84.6%) of studies reported that patients preferred oral administration.[132] Oral treatments were preferred owing to their increased ease of administration and ability to self-administer from home, reducing the need to travel to infusion clinics.[132] Further to this, the survey conducted by Yong *et al.* (2021), described above, found caregivers prefer treatments that are quick to administer.[131] These patient and caregiver preferences for a novel treatment with a convenient oral method of administration that is quick to administer are not captured in the QALY calculations.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Face validity

Model validations were performed in alignment with best practices.[133] Of note, a thorough clinical validation process was conducted in order to inform survival analysis for the PFS, OS and TTD extrapolations selected for the base case analysis.

Internal validity

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

External validity

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 71. It can be observed from this comparison that the median PFS prediction for selpercatinib closely aligns with the trial ([redacted] vs 26.15 months, respectively) whereas the model overestimates PFS for both comparators. Similarly, while the median OS prediction for selpercatinib is higher than the median OS derived from LIBRETTO-001 ([redacted] vs 47.57 months, respectively), the overestimation for OS is proportionally greater for both comparators. Together, these comparisons suggest that any misalignment between the predicted model outcomes and observed trial outcomes is likely to result in the model underestimating the benefit provided by selpercatinib in the real-world as compared with docetaxel monotherapy or docetaxel in combination with nintedanib.

Table 71: External validation of model outcomes against published PFS and OS estimates (months)

	Trial mPFS	Predicted mPFS	Trial mOS	Predicted mOS
Selpercatinib	26.15 (LIBRETTO-001)	[redacted]	47.57 (LIBRETTO-001)	[redacted]
Docetaxel monotherapy	2.8 (TA347)	[redacted]	10.3 (TA347)	[redacted]
Nintedanib+docetaxel	4.2 (TA347)	[redacted]	12.6 (TA347)	[redacted]

Abbreviations: ITT: intent-to-treat; mOS: median overall survival; mPFS: median progression free survival.
Sources: TA347[5]

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

In order to assess the cost-effectiveness of selpercatinib versus relevant comparators in patients with previously treated *RET*-fusion positive, advanced NSCLC in the UK, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England. As discussed further in Section B.3.6, a severity modifier of 1.7 on the QALY has been considered in all presented cost-effectiveness results given the considerable unmet need in this patient cohort, the alignment of the willingness-to-pay threshold under which the previous appraisal for selpercatinib in pre-treated *RET* fusion-positive advanced NSCLC (TA760) was conducted, and the proximity of the proportional shortfall calculated to the threshold for the 1.7x modifier to apply. In addition, the NICE end-of-life criteria were met in the previous appraisal for selpercatinib in pre-treated *RET* fusion-positive advanced NSCLC (TA760), resulting in a willingness-to-pay threshold approximately equivalent to the application of a 1.7x QALY modifier.[2]

The base case probabilistic ICERs for selpercatinib versus docetaxel monotherapy and versus nintedanib with docetaxel chemotherapy were £36,831 and £32,836, respectively, including a severity modifier of 1.7 on the QALY. The probabilistic and deterministic base case results were in close alignment and the deterministic sensitivity analysis results identified a small number of key influential parameters, and scenario analyses conducted to address sources of uncertainty in the model demonstrated that there was limited variation in the ICER. Together, these results indicate that the model is robust to parameter uncertainty. Furthermore, the economic results show that selpercatinib is associated with considerable QALY gains via improving PFS and OS: the incremental QALYs for patients receiving selpercatinib are estimated to be [redacted] and [redacted] versus docetaxel monotherapy and versus nintedanib with docetaxel chemotherapy, respectively, following the application of a severity modifier of 1.7.

Strengths

A robust clinical validation exercise was conducted by Eli Lilly with an expert oncologist practising in the UK in order to validate key inputs and assumptions, including survival extrapolations for OS, PFS and TTD.[6] In addition, the clinical expert reviewed the baseline characteristics of patients enrolled in the LIBRETTO-001 trial and comparator choice in the model, both of which were subsequently deemed to be representative of UK clinical practice.[6] The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of selpercatinib into NHS clinical practice.

Survival data from the LIBRETTO-001 are now available from a larger population of patients with a longer follow-up period, resulting in survival data which are considerably more mature than those presented in TA760, reducing the uncertainty associated with data immaturity previously outlined.[2] These survival data are consistent with those reported previously and demonstrate a sustained benefit to patients across a range of domains.

The cost-effectiveness analysis is associated with several strengths, the first being that many new therapies for NSCLC and those targeting genetic alterations, have been appraised by NICE. A review of relevant NICE evaluations was conducted during model design and development, and thus it was possible to take into account a number of learnings from previously developed models for NSCLC, in addition to prior external assessment group (EAG) and Committee preferences for methodological approaches in this area, such as cost and resource use and the

selection of HSUVs. In particular, Committee preferences from the prior NICE appraisal of selpercatinib in this indication (TA760) have been considered throughout the model.

The model further closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully capture and discounting costs and benefits at a rate of 3.5% per annum.[134]

Limitations

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

As discussed in Sections B.2.9, in order to connect the selpercatinib arm to the NMA and produce relative efficacy versus both comparators relevant to the decision problem, it was necessary to generate a pseudo-control arm using IPD for the docetaxel monotherapy arm of the REVEL trial.[94] This pseudo-control arm was subsequently used as a reference in the survival analysis for the cost-effectiveness model to generate PFS and OS extrapolations for nintedanib plus docetaxel chemotherapy. To minimise uncertainty in this process, the pseudo-control arm was adjusted for prognostic factors through use of propensity score matching, thus accounting for key differences in characteristics between the LIBRETTO-001 and REVEL trial populations and generating a reliable treatment effect estimate for the two treatments.

A further potential limitation of the relative efficacy estimates is that efficacy data for both relevant comparators was derived from trials conducted in patient populations in whom *RET* fusion was not specifically tested for/reported. However, as described in Section B.1.3.1, an analysis of 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761), found that after adjusting for baseline covariates, no statistically significant prognostic effect of *RET* fusion status on PFS or OS was identified.[25] This evidence supports the approach undertaken for the indirect comparison whereby known prognostic factors have been adjusted for, thus minimising uncertainty in the analysis.

Conclusion

Selpercatinib is currently available via the CDF for treatment of patients with previously treated, advanced, *RET* fusion-positive NSCLC.[2] However, if selpercatinib was not recommended by NICE for routine commissioning, there would be a considerably high unmet need amongst adult patients with previously treated *RET*-fusion positive advanced NSCLC for a safe, targeted treatment option with a convenient method of administration. Selpercatinib has demonstrated superior efficacy to relevant comparators in UK clinical practice (Section B.2.9) which, as demonstrated in the LIBRETTO-001 trial, is associated with improved patient HRQoL. With its targeted mechanism of action, oral method of administration and tolerable safety profile, selpercatinib could continue to be a valuable treatment option for these patients, as demonstrated by the considerable incremental QALYs associated with selpercatinib versus both comparators in the cost-effectiveness analysis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for previously treated *RET* fusion-positive advanced non-small cell lung cancer [ID6293]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID6293_Selpercatinib in 2L RET fusion-positive NSCLC_SIP_12Apr24_NoCON	V1.0	No	12th April 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Selpercatinib; **brand name**: Retsevmo®

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

The population that this treatment will be used for is people with advanced ***RET*** **fusion-positive non-small cell lung cancer** (**NSCLC**) who have received one or more prior therapies (are "previously treated") for the condition.

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

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

Selpercatinib currently holds a conditional **marketing authorisation** from the UK regulator (Medicines and Healthcare products Regulatory Agency, MHRA) as a stand-alone therapy for the treatment of patients with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor. This was granted in March 2021 for patients who require

systemic treatment following prior treatment with immunotherapy and/or platinum-based chemotherapy, and in October 2022 was extended to cover previously untreated patients.[1]

The approval can be accessed via the following link: https://mhraproducts4853.blob.core.windows.net/docs/6c772ac4d0c41432c8e3241e484b19cd57a47d89. More information on this can be found in **Document B** in **Section B.1.2**.

This submission focusses on the treatment of previously treated patients only, because the use of selpercatinib in untreated disease (**first-line**) is already approved separately by NICE (TA911).[2]

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

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

- Roy Castle Lung Cancer Foundation Global Lung Cancer Coalition – Financial contributions made in 2024, 2023, 2022, 2021 and 2019
- United Kingdom Lung Cancer Coalition Corporate Membership – Financial contribution made in 2021
- Mesothelioma UK Stand Sponsorship – Financial contribution made in 2019

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

The main condition that selpercatinib plans to treat is non-small cell lung cancer (NSCLC)

What is NSCLC?

Cancer that first develops in the lungs is classified as either small cell lung cancer or non-small cell lung cancer (NSCLC), depending on the relative size of the cancer cells when viewed under a **microscope**.[3] As the name suggests, cancer cells of small cell lung cancer appear small and round under a microscope, whilst NSCLC cancer cells are larger.[4] NSCLC is the most common type of lung cancer in the United Kingdom (UK), accounting for 80–85% of lung cancer cases.[3]

NSCLC is also classified by the presence of changes to specific **genes** within the cancer cells.[5] A **genetic alteration** that occurs in 1–2% of NSCLC cases is the joining together, or '**fusion'**, of a gene named '*RET*' with another independent gene.[6] This genetic change drives growth of the tumour. This is described further below.

For the purposes of treatment, lung cancers can be classified further by the presence of '**biomarkers**', which in this case are **proteins** present on the tumour. Of particular relevance to the treatment of NSCLC is the presence or absence of the **programmed death-ligand 1** (**PD-L1**) biomarker, which is described further in Section 2c.

What are the signs and symptoms of NSCLC?

Symptoms associated with NSCLC are often general and could be associated with a wide range of different conditions, both mild and serious. NSCLC symptoms also vary from patient to patient. As a result, NSCLC is often diagnosed at an advanced stage, which is when cancer that originated in the lung has spread to other organs: 71% of patients diagnosed with NSCLC in England in 2020 were diagnosed at an advanced stage of disease.[7]

Common physical symptoms associated with NSCLC are:[8, 9]

- Fatigue (98%)
- Loss of appetite (98%)
- Trouble breathing (94%)
- Cough (93%)
- Pain (90%)
- Coughing up blood (70%)

What is *RET* fusion-positive NSCLC?

Fusion of the *RET* gene with another gene leads to the production of a protein (the RET protein) that is active all the time, including at times when it would usually have been inactive. This overactivity of the RET protein results in rapid and uncontrolled growth of cancer cells, leading to the development of a tumour in the lungs.[10] The *RET* fusion gene also enables the cancer cells to survive in conditions when healthy cells would die.[10]

The *RET* fusion gene leads to the development of blood vessels around the tumour, to enable the tumour to grow.[10] This development of a network of blood vessels around the tumour increases the likelihood of cancer cells spreading to other parts of the body via the bloodstream.[10]

How many people get *RET* fusion-positive NSCLC?

Lung cancer is the second most common cancer in England, accounting for approximately 13% of all newly diagnosed cancers, with 37,237 people being newly diagnosed with lung cancer in 2020.[7, 11] NSCLC accounts for the majority (80–85%) of lung cancer cases in the UK.[3] Of the patients diagnosed with NSCLC, 1–2% have *RET* fusion-positive NSCLC.[6] This equates to approximately 150 adults being diagnosed with advanced NSCLC who are *RET* fusion-positive in England and Wales each year.[6, 12, 13]

Unlike other types of lung cancer, patients with *RET* fusion-positive NSCLC are typically of a younger age (65 years or younger) with minimal or no prior history of smoking.[14, 15] *RET* fusions in NSCLC tumours have also been found to be associated with female gender and Asian ethnicity.[6]

What is the disease burden of NSCLC for patients?

Physical impact:

Disease symptoms caused by NSCLC, and the side effects of therapies used to cure or manage them, impact patients both physically and emotionally.[8, 16]

In advanced stages of NSCLC, the cancer has spread to other parts of the body in a process called metastasis. Metastasis causes additional symptoms associated with the development of new tumours.[17] The cancer of patients with *RET* fusion-positive NSCLC frequently spreads to the brain, which causes confusion, headaches and changes in behaviour, significantly impacting the emotional state of patients.[18]

The point at which a patient is diagnosed can affect the outcome of treatment. More than half (57%) of patients diagnosed in the early stages of NSCLC will live for five years or longer, whilst only 3% of patients diagnosed with advanced disease will live for as long.[19]

Emotional impact

The mental wellbeing of patients is reported to be negatively affected after receiving a lung cancer diagnosis, receiving treatment or having conversations about the long-term outlook (**prognosis**) of patients. As a result, between 23–40% of patients with NSCLC are affected by depression, and an estimated 16–23% of patients are affected by anxiety.[8]

Impact on quality of life

The accumulation of the physical and emotional impacts of NSCLC make patients increasingly unable to complete normal activities. As a result, the **quality of life** (the overall enjoyment of life) of patients with NSCLC is lower than that of the general

population.[20] The quality of life of patients with NSCLC declines as the disease becomes more advanced and patients experience an increasing number of worsening symptoms.[21]

What are the financial and societal costs of NSCLC?

Financial cost

The financial cost of lung cancer to the economy in England was estimated to be £307 million in 2010 through direct costs to the National Health Service (NHS) and indirect costs to society.[22] Direct costs to the NHS include costs associated with medication, surgery, **radiotherapy**, follow-up visits and the management of **side effects** related to treatment. Treatment costs increase as NSCLC progresses and becomes more advanced. In 2014, treatment costs associated with early NSCLC were £7,952 per patient, whereas treatment costs associated with the most advanced stage of NSCLC were £13,078 per patient.[23]

Societal cost

Due to the impact of NSCLC on patients' mental and physical health, the work life of patients is negatively impacted by NSCLC. This leads to costs to society through increased work absenteeism, lost productivity at work and some patients taking early retirement.[24]

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

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is NSCLC diagnosed?

At early stages of NSCLC, the symptoms patients experience are non-specific and do not point to NSCLC as an obvious causative factor.[7] As a result, most people with early-stage NSCLC are unaware that they have the condition, so the cancer grows rapidly in the absence of treatment and progresses to a more advanced stage of disease.[25, 26] Advanced stages of NSCLC are associated with a greater number of worsening symptoms, which interferes with patients' abilities to carry out normal daily tasks, causing patients to seek medical attention.[8]

People with symptoms of NSCLC receive an imaging scan, such as a chest **X-ray**, **computerised tomography** (**CT**) **scan** or **magnetic resonance imagining** (**MRI**) **scan**, which looks at the area around the lungs to identify if there are any abnormalities and to see if the cancer has spread. If lung cancer is suspected, patients may be asked to undergo further tests, including a **biopsy**, in order to identify the specific type of lung cancer (e.g. NSCLC) as well as any abnormal genes that might be driving the cancer.[27]

To identify any changes to specific genes which might be driving the cancer (such as *RET*), patients will need to undergo genetic testing. This involves screening genetic material inside the patient's cancer cells to identify the presence of a genetic abnormality. The NHS has established Genomic Hubs where genetic testing is routinely practiced for patients with newly diagnosed lung cancer. A technique called **next generation sequencing** (**NGS**) is used at the Genomic Hubs to identify whether cancer cells have abnormal genes. NGS is the diagnostic standard for identifying abnormal genes, such as *RET* fusions, within NSCLC.

Staging

The prognosis of patients with NSCLC is highly dependent upon disease stage at diagnosis. NSCLC can be categorised into four principal stages, stages I–IV, with stage IV being the most advanced stage of disease, linked to the worst long-term outcomes for patients.[28] Stages IIIB–C and IV are grouped under the classification of 'advanced' disease.[28, 29] Patients with advanced *RET* fusion-positive NSCLC are the target population of selpercatinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

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

What are the current treatment options for patients with advanced second-line NSCLC?

In England and Wales, guidance for the management of lung cancer is provided by the National Institute for Health and Care Excellence (NICE), via the document NG122, available here: https://www.nice.org.uk/guidance/ng122.[30]

Many patients with NSCLC require therapy with more than one treatment option, either due to the first treatment option they try (the first-line treatment) not working sufficiently and their disease progressing whilst receiving this treatment, or due to the side effects they experienced on treatment being too severe, causing them to stop taking the drug.

Selpercatinib is being positioned for use in this **second-line** or later setting – all patients who would be treated with selpercatinib would have received at least one previous treatment. In contrast to the treatment of earlier stage disease, treatments aiming to cure the patient are not suitable for patients who progress to advanced (Stage IIIB/C or IV) NSCLC, or who have advanced NSCLC at the time they are diagnosed. Instead, therapies aiming to delay disease progression and extend survival for as long as possible are recommended for those with advanced disease.

Patients with no targetable gene mutations

For patients with advanced NSCLC with no identified genetic changes, NICE recommends several therapy options following discontinuation of their first-line treatment. Clinician choice of which treatment is suitable to prescribe depends on various factors, including the status of specific biomarkers in the cancer. One such biomarker is called PD-L1, overactivity of which blocks the body's **immune system** from killing cancer cells.

Selection by clinicians in the UK about which treatment might be suitable to prescribe to a patient with advanced second-line NSCLC who has no specific gene mutations may be based on this PD-L1 score, as summarised in Table 1 and below:

- Chemotherapies: Patients may receive chemotherapy treatments on their own, such as pemetrexed or docetaxel. Alternatively, patients may receive combination therapies where several treatments are given together, such as platinum doublet chemotherapy, pemetrexed plus carboplatin, or docetaxel plus nintedanib. These chemotherapy treatments may be offered to all patients regardless of their PD-L1 level.[31]
- Immunotherapy: **Immunotherapy** treatments work by programming the body's own immune system to recognise and kill the cancerous cells. For second-line patients with advanced NSCLC without a specific genetic mutation and a PD-L1 level of 1% or more, two immunotherapy options are recommended: pembrolizumab and nivolumab. A further immunotherapy, atezolizumab, is recommended in patients with advanced NSCLC without a specific genetic mutation and regardless of PD-L1 level.[32-36]
- Best supportive care: If no other treatments are deemed suitable, patients could receive best supportive care.

Table 1: Types of therapy recommended for previously treated, advanced NSCLC

Patient Group	Type of Therapy
Patients with no targetable gene mutations or biomarkers (e.g. PD-L1 status)	• Atezolizumab[37] • Docetaxel with nintedanib[38] • Docetaxel[30] • Pemetrexed in combination with carboplatin[30] • Platinum doublet chemotherapy[30] with or without subsequent pemetrexed maintenance therapy[39, 40] • Best supportive care[30]
Patients with a PD-L1 biomarker level of more than 1%	• Pembrolizumab[41] • Nivolumab[42]

Abbreviations: PD-L1: programmed death ligand-1.

Patients with a specific targetable gene mutation

If patients have an identified genetic marker, it is standard clinical practice in the UK for them to receive a treatment that is targeted to that genetic marker, rather than relying on the status of a biomarker such as PD-L1. Therefore, if it were recommended, it is expected that all patients with previously treated *RET* fusion-positive NSCLC would be eligible to receive selpercatinib regardless of their PD-L1 status, as this drug is the only treatment that specifically targets and kills *RET* fusion-positive cancer cells.[2]

Treatments targeted to various other gene mutations, distinct from *RET* fusion, are currently recommended for use in typical UK clinical practice. However, it is extremely rare for patients to have more than one gene mutation at a time.[43-45] Furthermore, immunotherapies (atezolizumab, nivolumab and pembrolizumab) would most likely be given to patients as a first-line treatment, meaning that patients would not then receive them again in the second-line setting, and platinum doublet chemotherapy is also rarely used in the second-line setting.[46] Therefore, it is not expected that patients with *RET* fusion-positive NSCLC would receive any of these, so these are not discussed further in this document. For this reason, in this appraisal, the relevant comparators for selpercatinib are docetaxel chemotherapy, and docetaxel in combination with nintedanib.

Currently, patients in England and Wales with *RET* fusion-positive NSCLC can be offered selpercatinib as a treatment option in the second-line or later (after at least one previous treatment has failed).[46] However, when this recommendation was made, NICE considered that there was some uncertainty around the long-term effects of selpercatinib. For this reason, NICE granted short-term conditional reimbursement, until such time as it considers the evidence to be sufficient to grant a full reimbursement, which is the aim of this submission. Regardless of the outcome of this submission, patients already being treated with selpercatinib would not be taken off the treatment. Should NICE recommend use of selpercatinib as a therapy for patients with previously treated advanced *RET* fusion-positive NSCLC, it would remain the only available therapy which specifically targets and kills cancer cells with abnormal *RET* gene fusions.

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

Context:

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

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

NSCLC from the patient perspective

Patients with NSCLC are often diagnosed at an advanced stage of disease as a result of the symptoms they experience at earlier stages of disease being general and non-specific. Unlike early stages of NSCLC, advanced NSCLC is not treated with the aim of curing it entirely. Instead, treatment of advanced NSCLC aims to increase survival of patients for as long as possible. As NSCLC becomes more advanced, the quality of life of patients declines as they experience increasing numbers of worsening symptoms and undergo treatment which can cause mild to severe AEs.

A summary of three studies investigating the quality of life of patients with NSCLC is provided below.

Global Lung Cancer Coalition, 2021 Patient Experience Survey (UK)[47]

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

Patient preferences for treatment of metastatic NSCLC (Yong et al., 2021)[48]

A survey investigating preferences for treatment of advanced NSCLC in 308 patients and 188 caregivers was conducted. The survey found patients valued treatments that increased their survival as well as those which were not associated with side effects that may lead to hospitalisation. The survey in caregivers of patients with advanced NSCLC valued treatments which are quick to administer and have low frequency of administration.

Patient-reported preference for oral versus intravenous administration for the treatment of cancer (Eek et al., 2016)[49]

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

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment? Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Selpercatinib is an anti-cancer therapy that targets cancer cells that are growing and dividing uncontrollably as a result of a *RET* gene fusion (see below).[50] It works by preventing cell growth and division in these cancer cells in order to inhibit tumour growth.

RET fusion-positive NSCLC tumours are driven by the joining together, or 'fusion', of the '*RET*' gene with another independent gene.[6] The *RET* gene provides instructions for making a protein called 'RET' which is needed for cell growth and division.[51] When the *RET* gene becomes fused to another gene, the resulting RET protein is joined to another protein.[52] This abnormal, fused RET protein is in a permanently 'activated state', meaning that it will continue to enable the cancer cells to grow in an uncontrolled manner.[52] Uncontrolled cell growth leads to the development of tumours. Selpercatinib works by inhibiting the abnormally fused RET protein, thereby reducing levels of uncontrolled cell growth and division.

Innovation in patient care

Selpercatinib is the only **targeted treatment** currently available in NHS clinical practice for advanced *RET* fusion-positive NSCLC that has been previously treated. The specificity of a targeted treatment such as selpercatinib is anticipated to result in better survival outcomes and to cause fewer side effects, compared to existing non-targeted treatments.

Indeed, selpercatinib has shown meaningful treatment responses in the LIBRETTO-001 trial, reducing tumour size and slowing down disease progression in patients who have previously treated advanced *RET* fusion-positive NSCLC (as explored in **Section 3e**). The median **progression-free survival** (**PFS**; the length of time before the cancer worsens to become more advanced) was 24.9 months and 61% of patients experienced a reduction in tumour size.

In addition, the LIBRETTO-001 trial demonstrates that selpercatinib is associated with a well-**tolerated**, clinically manageable safety profile, with only 3% of patients discontinuing treatment due to side effects caused by selpercatinib.[53]

If selpercatinib were no longer recommended by NICE in the second-line setting for the treatment of advanced *RET* fusion-positive NSCLC, these patients would lose access to the only targeted treatment for this gene alteration. Instead, patients would receive the same non-targeted second-line treatment options as patients with no recognised

oncogenic drivers. This would represent a significant unmet need in these patients for a clinically-effective, targeted treatment option with a tolerable safety profile.

3b) Combinations with other medicines

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

- No

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

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

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

No – selpercatinib is intended for use as a standalone therapy and therefore does not need to be used in combination with other medicines for NSCLC.

3c) Administration and dosing

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

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

How is selpercatinib taken?

Selpercatinib is administered orally, twice daily via a tablet. As such, selpercatinib can be self-administered by patients at home, providing a convenient treatment option to patients.[54]

How much medicine do patients take and when?

The recommended starting dose of selpercatinib is based on the body weight of the patient. For patients who weigh 50 kg (110.23 lb) or more, the recommended dose is 160 mg of selpercatinib twice a day, administered orally as 80 mg capsules (total dose per day is 320 mg). For patients who weigh less than 50 kg (110.23 lb), the recommended dose is 120 mg of selpercatinib twice a day (total dose per day is 240 mg). Capsules are also available in 40 mg dosages for patients who require a reduced dose as a result of side effects to selpercatinib.[50]

Patients should take the doses at approximately the same time every day. The capsules should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing) and can be taken with or without food. If a patient misses a dose of selpercatinib or vomits, they should not take an additional dose. The patient should take the next dose of selpercatinib at the scheduled time.[50]

Patients are recommended to continue treatment until their cancer progresses or they experience unacceptable toxicity (e.g. unacceptable side effects), following medical advice. Further details on the administration and dosing requirements for selpercatinib can be found in the Summary of Product Characteristics (SmPC) for selpercatinib for the treatment of advanced *RET* fusion-positive NSCLC who require systemic treatment following prior treatment with immunotherapy and/or platinum-based chemotherapy which can be accessed via the following link: https://mhraproducts4853.blob.core.windows.net/docs/6c772ac4d0c41432c8e3241e484b19cd57a47d89

3d) Current clinical trials

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

Studies of selpercatinib in advanced *RET* fusion-positive NSCLC

Selpercatinib for the treatment of advanced *RET* fusion-positive NSCLC who have been previously treated for the condition has been evaluated in one **clinical trial**, LIBRETTO-001. The trial investigates the effectiveness and safety of selpercatinib in patients with a variety of *RET* fusion-positive tumours, including NSCLC.

LIBRETTO-001 is a clinical trial made up of two phases, **Phase I** and **Phase II**. During Phase I, the dose of selpercatinib that healthy volunteers were exposed to was increased throughout the trial to determine the optimal dose for maximising the therapeutic effect of the drug whilst also preventing unmanageable side effects. During Phase II of the trial, patients with advanced *RET* fusion-positive NSCLC who have been previously treated for the condition were exposed to dose of selpercatinib identified during Phase I to determine whether the dose is effective and safe in the patient population.

The Phase II part of the LIBRETTO-001 trial included patients with advanced *RET* fusion-positive NSCLC, which meant patients had to meet some specific criteria to take part in the trial, including:

- Adult patients (at least 18 years of age)
- Patients with an advanced solid tumour that has progressed or was non-responsive to available therapies and for which no standard or available curative therapy exists
- Evidence of a *RET* gene alteration in the tumour and/or blood
- Life expectancy of at least 3 months

A summary of the key information about the LIBRETTO-001 trial is provided in **Table 2**. While overall study completion is anticipated in 2026, no further data from the NSCLC population are anticipated.

Table 2. Trials investigating selpercatinib

Trial name and number	Location	Number of patients included	Expected trial completion date
LIBRETTO-001 **(NCT03157128)**	Worldwide (US, Australia, Canada, Denmark, France, Germany, Israel, Italy, Japan, Republic of Korea, Singapore, Spain, Switzerland, Taiwan and UK)	796 patients with a variety of *RET* fusion-positive cancers. 356 patients with *RET* fusion-positive NSCLC **247 patients with previously treated *RET* fusion-positive NSCLC**	28th February 2026

Abbreviations: UK: United Kingdom; US: United States.

More information about LIBRETTO-001 can be found here:

- Drilon *et al*., 2023[53] (https://doi.org/10.1200/JCO.22.00393)
- ClinicalTrials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT03157128#contacts)

3e) Efficacy

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

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

Trial results

In the LIBRETTO-001 trial, the **efficacy** (effectiveness) of selpercatinib was measured according to how well it improved three key things:

- **Tumour response:** This was measured by recording the physical size of tumours and seeing if they decreased in size over the course of treatment with selpercatinib. 61% of patients with previously treated advanced *RET* fusion-positive NSCLC experienced a reduction in tumour size[53]
- **Progression-free survival (PFS):** PFS is a measure of how long a patient continues to live with a disease after beginning treatment, without the disease getting worse (progressing). At the point where the median time since starting the trial (follow-up time) was 24.7 months, the median PFS for patients with previously treated advanced *RET* fusion-positive NSCLC was estimated to be 24.9 months[53]
- **Overall survival (OS):** OS is a measure of how long a patient remains alive after they start treatment. At a median follow-up of 26.4 months, 87.9% of patients were estimated to be alive after one year of treatment with selpercatinib, 68.9% of patients after two years of treatment and 58.5% of patients after three years of treatment[53]

More efficacy results can be found in **Document B**, **Section 2.6.** (**subsections B.2.6.1.**, **B.2.6.2**, **B.2.6.3.** and **B.2.6.4.**).

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

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

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

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

Quality of life impact of selpercatinib

The quality of life impact for patients receiving selpercatinib was also assessed in the LIBRETTO-001 clinical trial. Quality of life was measured using a questionnaire that was completed by patients at multiple time points before, during and at the end of the trial. The questionnaire that was used in LIBRETTO-001 is called the European Organisation of Cancer Research Quality of Life Questions C30 (EORTC QLQ-C30).[55] This questionnaire evaluates several areas that impact the quality of life of patients with cancer, including physical, emotional, cognitive and social functioning, as well as symptoms and financial status.[55]

In most of the quality-of-life areas assessed using the questionnaire, a higher proportion of patients with advanced *RET* fusion-positive NSCLC experienced improved or stable, rather than worsening, quality of life following treatment with selpercatinib.[56] As a result, treatment with selpercatinib may help to improve and prolong quality of life for patients by delaying progression of the cancer and thus preventing the associated worsening of disease symptoms.

In comparison, patients receiving chemotherapy for NSCLC (the current standard of care for this population) typically show reduced quality of life scores following treatment. This is due to the associated toxicity of treatment caused by the lack of targeted action of chemotherapy.[57] A study in 58 patients with NSCLC receiving chemotherapy found that overall quality of life decreased significantly from 100 to 91 ($p=0.03$) following two rounds of chemotherapy.[58] Increased pain, decreased physical activity and increased ease of becoming unwell were key areas contributing towards patients decreased quality of life following treatment with chemotherapy.[58]

In addition, selpercatinib is administered orally rather than intravenously like some of the commonly used chemotherapies and immunotherapies.[54] This means that self-administration at home is possible, which is more convenient for patients, thus reducing the disease burden.

3g) Safety of the medicine and side effects

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

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own side effects, and the same medicine can produce different reactions in different people. The SmPC for selpercatinib reports side effects which are categorised as very common (occurring in more than 1 in 10 people) and common (occurring in more than 1 in 100 but less than 1 in 10 people). Very common side effects associated with selpercatinib include: decreased appetite, headache, dizziness, QT interval prolongation (an extended time between contraction and relaxation of the heart), hypertension (high blood pressure), abdominal pain, diarrhoea, nausea, vomiting, constipation, dry mouth, rash, pyrexia (fever), oedema (a build-up of fluid in the body causing swelling), increase in alanine transaminase (ALT) and aspartate aminotransferase (AST) (values related to liver health), decreased platelets, decreased lymphocyte (white blood cells) count, decreased magnesium, decreased creatinine and haemorrhage (internal or external blood loss). The only common side effects associated with treatment with selpercatinib are hypersensitivity (an immune reaction such as those caused by allergies) and interstitial lung disease/pneumonitis. The very common and common side effects were found to be easily managed by either stopping treatment with selpercatinib or reducing the dose of selpercatinib given to patients.[59]

In the LIBRETTO-001 trial, selpercatinib was generally well tolerated in patients with a range of different *RET* fusion-positive cancers (including NSCLC). The side effects of selpercatinib were predictable and could be easily managed through reducing the dose of selpercatinib taken or delaying taking the next dose of the drug**.** The most common side effects, which affected more than or equal to 20% of patients with any *RET* fusion-positive tumour type in the LIBRETTO-001 trial, are summarised in **Table 3**. The proportion of these patients who experienced a more serious side effect during the LIBRETTO-001 trial is shown in **Table 4**.

Table 3: Summary of the most common side effects experienced by patients in the LIBRETTO-001 trial

Side effect	Patients with this side effect in LIBRETTO-001 (N=796), %
Oedema	48.5
Diarrhoea	47.0
Fatigue	45.9
Dry mouth	43.2
Hypertension	41.0
Aspartate transferase (AST) increased	36.7
Alanine aminotransferase (ALT) increased	35.7
Abdominal pain	33.7
Constipation	32.8
Rash	32.8
Nausea	31.2
Blood creatinine increased	28.5
Headache	27.6
Cough	23.1
Dyspnoea	22.5

Vomiting	22.4
ECG QT prolongation	21.1
Arthralgia	20.7

Note: further explanation of the terms in **bold** are provided in the glossary (Section 4b).
Source: Drilon *et al.* J Clin Oncol (2023).[53]

Table 4: Summary of serious side effects in the LIBRETTO-001 trial

Side effect	Patients with this side effect in LIBRETTO-001 (N=796), %
Hypertension	19.7
Alanine aminotransferase increased	11.4
Aspartate transferase increased	8.8
Diarrhoea	5.0
ECG QT prolongation	4.8
Fatigue	3.1
Dyspnoea	3.1
Abdominal pain	2.5
Blood creatinine increased	1.9
Vomiting	1.8
Headache	1.4
Nausea	1.1
Constipation	0.8
Oedema	0.7
Rash	0.6
Arthralgia	0.3
Dry mouth	0.0
Cough	0.0

Note: The table above shows the percentage of patients in the LIBRETTO-001 trial who experienced a side effect of severity grade 3 or greater. Side effects are usually given a grade to indicate their severity. A grade 1 side effect is mild and the least severe grade. A grade 3 side effect is a severe side effect, which may require hospitalisation, but is not immediately life threatening. A grade 4 side effect is life threatening and is the most severe grade given to side effects.
Source: Drilon *et al.* J Clin Oncol (2023).[53]

Managing side effects

In the LIBRETTO-001 trial, selpercatinib was generally well-tolerated by patients with *RET* fusion-positive cancers. Patients with NSCLC in the LIBRETTO-001 trial experienced side effects which were well-characterised and predictable.[53] The side effects could be managed and reversed easily by patients either reducing or delaying the next dose of

selpercatinib that they received, or by taking other medications to treat the side effects.[59] Hypertension (high blood pressure) was the most common serious side effect, but it was easily managed and did not result in large dose reductions or delayed doses of selpercatinib.[53]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

The key benefits of selpercatinib to patients with advanced, *RET* fusion-positive NSCLC that has been previously treated include:

Selpercatinib represents a highly effective treatment option for patients with a rare gene alteration. In the LIBRETTO-001 trial, selpercatinib has been shown to reduce tumour size in 61% of patients, slow down disease progression (median PFS of 24.9 months with a median follow-up of 24.7 months) and improve survival in patients (87.9% of patients were estimated to be alive after 1 year of treatment).[53]

Selpercatinib has an improved safety profile compared to existing treatments which are used for managing advanced *RET* fusion-positive NSCLC, such as immunotherapy and chemotherapy. Immunotherapy and chemotherapy are untargeted treatment options, meaning they can affect multiple organ systems and cause serious side effects. Serious side effects have been shown to occur in 7–13% of patients treated with immunotherapies.[60] Serious side effects of experienced by patients receiving immunotherapy or chemotherapy detrimentally impact patients' quality of life. The improved effectiveness and safety profile of selpercatinib compared to existing treatments is anticipated to translate into improvements in patients' quality of life. Data collected using a quality of life assessment tool as part of LIBRETTO-001 found selpercatinib treatment results in improvements in patients' quality of life, including physical, emotional, cognitive and social functioning scores, as well as symptom and financial status scores.[56]

Selpercatinib is administered orally, rather than intravenously like some of the commonly used chemotherapies and immunotherapies. This means that self-administration at home is possible, which is often preferable for patients due to its more convenient method of administration.[49]

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

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Selpercatinib is generally well-tolerated and effective, leading to tumour shrinkage, disease control and survival benefits in some patients. However, while selpercatinib has the potential to satisfy an unmet need amongst patients with previously treated *RET* fusion-positive NSCLC, some things that patients may want to consider before starting treatment include:

Efficacy

Selpercatinib is the only treatment available through NHS clinical practice that specifically targets abnormal RET fusion proteins in advanced *RET* fusion-positive NSCLC. As a result, selpercatinib has the potential to extend patients' lives more than other available treatments, however, the extent to which selpercatinib extends lives differs from patient to patient. Patients for whom selpercatinib does not work may still experience side effects, which are detailed further below.

Side effects

As outlined in **Section 3g**, the summary of product characteristics for selpercatinib reports side effects which are categorised as very common (occurring in more than 1 in 10 people) and common (occurring in more than one in a hundred but less than one in ten people).[59] Very common side effects associated with selpercatinib include decreased appetite and headache. Common side effects associated with treatment with selpercatinib are hypersensitivity (an immune reaction such as those caused by allergies) and interstitial lung disease/pneumonitis (scarring or inflammation of the lungs which can cause shortness of breath and a dry cough).

The very common and common side effects associated with selpercatinib were found to be easily managed by either stopping treatment or reducing the dose of selpercatinib given to patients.[50] Overall, selpercatinib treatment is associated with a manageable safety profile due to its targeted mechanism of action, which reduces side effects caused by **off-target effects** (when a drug affects another pathway in the body in addition to the intended target). In addition, the side effects associated with selpercatinib are less severe than those associated with alternative treatments, such as existing chemotherapies.

Administration

Selpercatinib requires more regular administration than existing treatments in clinical practice (docetaxel, and docetaxel in combination with nintedanib therapy) which are administered via intravenous infusion. Selpercatinib tablets should be taken orally as an 80 mg capsule, twice daily (Section 3c). In contrast, docetaxel chemotherapy is administered intravenously every 3 weeks for 4 cycles.[61] Docetaxel in combination with nintedanib requires docetaxel to be delivered intravenously on day 1 of a 3 week cycle, for a total of 4 cycles, whilst nintedanib is taken as a 200 mg tablet twice daily.[62]

Caregiver preference studies found caregivers of patients with NSCLC valued treatments which could be administered more quickly and less frequently.[49] Patient preference studies revealed patients prefer oral therapies over those delivered intravenously due to their increased convenience and ease of administration (Section 2d).[49] These studies suggest that whilst the frequent administration requirements of selpercatinib may be somewhat of a disadvantage, its quick, oral method of administration has the potential to be of benefit both patients and their caregivers.

Monitoring

Another potential disadvantage of treatment with selpercatinib is that it requires additional monitoring to existing treatments in clinical practice. For example, after 1 week of treatment, patients have an **electrocardiogram** (**ECG**) to measure activity of the heart and **serum electrolytes** (molecules found in the liquid of the blood) are measured. Each of these measures are monitored at least monthly for the first 6 months of treatment. The frequency of monitoring thereafter should be adjusting based upon patients' risk factors including diarrhoea, vomiting, and/or nausea. Additionally, blood pressure, thyroid function and liver function are all required to be monitored periodically during treatment.[63]

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (selpercatinib) with the standard of care (docetaxel, and docetaxel in combination with nintedanib).

How the model reflects NSCLC

The economic model was designed to reflect the key features of NSCLC and clinical practice in the UK. To do this, a model structure called a partitioned survival model was chosen. The model itself was made up of three health states:

- Progression free (patients' disease is responding to treatment and is not actively progressing)
- Progressed disease (the patient's cancer has worsened)
- Death

These three health states reflect the three potential stages of health associated with advanced NSCLC. Reflecting the progressive nature of advanced NSCLC, the model did not allow patients to move from a worse level of health to an improved level of health.

Modelling how much selpercatinib improves PFS and OS

The results of the LIBRETTO-001 trial were used to inform the economic model. The main results from LIBRETTO-001 that were used in the model were PFS, OS and time to discontinuation of treatment. These were the main results used in the model because they were considered relevant to what would be considered a successful outcome when treating advanced NSCLC in clinical practice.

The results of the LIBRETTO-001 trial cover a total of 36.1 months, but the economic model simulates patients for the rest of their lifetime (25 years), a much longer period of time than the length of the trial. For OS and PFS, the longer-term results were predicted based on the available evidence (extrapolated). In addition, most patients will stop treatment for advanced NSCLC at some point, meaning that the model has to estimate the number of patients discontinuing their treatment for any time that is longer than the 36.1 months of the trial. In the model, this rate of discontinuation was estimated to be the same as the rate of patients discontinuing treatment during the trial.

Modelling how much selpercatinib improves quality of life

Individual health states (progression free, progressed and death) were each associated with a measurement of quality of life known as a utility value. Utility values take a numerical value between 0 to 1 (0 indicating death and 1 indicating perfect health). A

lower quality of life was modelled for patients in the progressed disease health state than in the progression-free health state. This reflects the fact that the mental and emotional impact of advanced NSCLC would be likely to be reduced when a patient experiences worsening of their disease. As selpercatinib is anticipated to improve PFS and OS compared to other available treatments for advanced NSCLC, this is expected translate into an overall higher modelled quality of life of patients receiving selpercatinib than comparators as the time patients are modelled to spend in the progression-free health state is increased.

The quality-of-life data that informed the model were from the LIBRETTO-001 trial. In this study, quality of life was measured using a questionnaire called EORTC QLQ-C30. This questionnaire evaluates several areas that impact the quality of life of patients with cancer, including physical, emotional, cognitive and social functioning, as well as symptoms and financial status.[55] The results of this questionnaire were then translated into utility values used in the model.

Modelling how the costs of treatment differ with the new treatment

Various cost categories are included in the model for the different treatments used for advanced NSCLC. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of monitoring needed once patients start the medicine
- The cost of other care received by patients alongside the medicine

These costs are considered for the new drug (selpercatinib) and for the old treatment options (docetaxel monotherapy, and nintedanib with docetaxel chemotherapy). Comparing these costs shows how the cost of treating patients is changed by selpercatinib being available to patients with previously treated *RET* fusion-positive NSCLC. As selpercatinib is an oral medicine, it is expected to be more convenient for patients and reduce costs relating to the administration of treatment. This is because other treatments available are given, at least in part, in hospital.

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in **Document B**, **Section B.3.9.2**. Variations of inputs in the model were tested and the results of these tests are explained in **Document B**, **Section B.3.11.4**.

Severity modifier

A **decision modifier** for cancer drugs called the “end-of-life criteria” was previously used to assess the benefits of treatments for diseases associated with short **life expectancy**. If the “end-of-life” criteria were met (people with the disease were expected to live less than 24 months *and* the new treatment was anticipated to extend their life by more than three months), then the NHS would consider accepting treatments even if the costs per health benefit gained were higher than would usually be considered. This may have been up to

£50,000 per health benefit (or **quality-adjusted life year [QALY]**) gained, rather than £20,000–£30,000. However, a new decision modifier was introduced from 2022 onwards for all types of illnesses. This is called the **severity modifier** and has replaced the end-of-life criteria which are no longer used. The following text explains the impact of the severity modifier on the economic analysis for selpercatinib.

Disease severity can be measured as the future health that would be lost by people with advanced NSCLC, compared with someone who does not have the condition. Benefits measured in terms of QALYs are valued more highly for severe diseases. The proportion of QALYs a patient with the condition is expected to lose compared to someone without the disease of the same age is calculated, and if this loss is large enough, then the QALYs expected to be gained from the new treatment are multiplied by 1.2 or 1.7 (i.e. the NHS is willing to pay more for these additional QALYs).

Using the health economic model, the company has calculated that a patient with advanced *RET* fusion-positive NSCLC following prior treatment would be expected to lose approximately 91–92% of expected QALYs. Based on this, and considering the large unmet need in this population, multiplying the QALYs by 1.7 is considered in the analysis.

Cost effectiveness results

Overall, the results of the cost effectiveness analysis show that treatment with selpercatinib was associated with higher costs, but also higher QALYs than docetaxel monotherapy or nintedanib plus docetaxel chemotherapy. This resulted in an **incremental cost-effectiveness ratio** (**ICER**) of £36,831 per QALY gained versus docetaxel monotherapy, and £32,836 per QALY gained versus nintedanib plus docetaxel chemotherapy. As explained above, these cost-effectiveness results take into account the severity of advanced *RET* fusion-positive NSCLC by multiplying the QALYs by 1.7 However, it should be noted that these results are based on company-preferred assumptions and do not account for any confidential discounts available for comparator treatments as these are not known to the company.

When considered in the context of a very advanced stage of disease with limited treatment options and extremely poor prognosis, the results of the economic analysis show that for the proposed group of patients to receive selpercatinib, it offers good value for money to the NHS when compared with currently available treatments. A recommendation for selpercatinib via routine commissioning would continue to offer this patient population an innovative, dedicated treatment option able to improve survival compared with existing treatment options.

Benefits of selpercatinib not captured in the economic analysis

Treatment with selpercatinib may have many different positive impacts for people with advanced NSCLC. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example:

- Selpercatinib is currently the only treatment available in NHS clinical practice that specifically targets the abnormal RET fusion protein in advanced *RET* fusion-positive NSCLC. The survival outcomes for patients with advanced NSCLC are

poor, with only 2.9% of patients diagnosed with advanced NSCLC surviving for 5 years or longer.[64] As well as physical disease symptoms that worsen with disease progression, patients with advanced NSCLC often suffer from depression and anxiety.[8] All these factors considered together negatively affect patients' quality of life. The availability of a treatment that is specifically targeted to RET, the driver of the development and survival of their cancer, may offer hope to patients and their families of delayed disease progression and improved survival. This hope is not captured in the calculations in the model.

- Another notable benefit of selpercatinib is that it has a convenient oral method of administration. Current alternatives to selpercatinib in UK clinical practice require intravenous infusion, and therefore need to be administered in a specialised infusion clinic, resulting in a greater economic burden on NHS resources. In addition, a review of the scientific literature reporting on patient preferences (including lung cancer patients) for oral compared to intravenous administration of cancer treatments by Eek *et al*. (2016) found the majority (84.6%) of studies reported that patients preferred oral administration.[65] Oral treatments were preferred owing to their increased ease of administration and ability to self-administer from home, reducing the need to travel to infusion clinics.[65] Further to this, the survey conducted by Yong *et al.* (2021), found that caregivers prefer treatments that are quick to administer.[48] These patient and caregiver preferences for a treatment with a convenient oral method of administration that is quick to administer are not captured in the quality-of-life calculations in the model.

Conclusion

The benefits outlined in **Section 3h** and the economic analysis results above suggest that selpercatinib represents good value for money and a good use of NHS resources as a treatment for patients with advanced *RET* fusion-positive NSCLC who have been previously treated for the condition.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Selpercatinib is an innovative treatment which would represent an important advancement in the treatment of advanced *RET* fusion-positive NSCLC

Selpercatinib is a targeted treatment

Advanced *RET* fusion-positive NSCLC is a condition that can have a significant effect on a patient's mental and emotional wellbeing and quality of life.[8] Despite this, selpercatinib is the only targeted treatment option available in NHS clinical practice that has been shown to be effective in patients with advanced *RET* fusion-positive NSCLC.[53]

All other available treatment options (docetaxel or docetaxel in combination with nintedanib) do not specifically target cancer cells containing the abnormal RET fusion protein that is present in *RET* fusion-positive NSCLC. As a result, docetaxel or docetaxel in combination with nintedanib are less effective options than selpercatinib at specifically targeting and killing cancer cells containing the abnormal RET fusion protein. Consequently, selpercatinib is anticipated to confer survival benefits to patients. Furthermore, as docetaxel (with or without nintedanib) do not specifically target *RET* fusion-positive cancer cells, they kill more healthy cells during treatment than selpercatinib, leading to uncomfortable or unpleasant side effects which detrimentally impact patients' quality of life. Conversely, as a targeted treatment, selpercatinib harms fewer healthy cells and thus causes fewer and less serious side effects in patients.

Selpercatinib has a convenient mode of administration

Finally, selpercatinib is administered orally, whereas existing treatments for advanced *RET* fusion-positive NSCLC that has been previously treated are administered via intravenous infusion.[31, 35, 50] A review of the scientific literature reporting patient preferences for oral compared to intravenous administration of cancer treatments (including lung cancer patients) found the majority (84.6%) of studies reported a patient preference for oral administration.[49] Reasons provided included increased ease of administration and convenience due to the ability to self-administer from home.[49] In addition, a survey investigating the preferences of caregivers of patients with advanced NSCLC found that caregivers prefer treatments that are quick to administer, thus showing selpercatinib fulfils an unmet need for a convenient oral treatment.[48]

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

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues anticipated in the use of selpercatinib in previously treated *RET* fusion-positive NSCLC.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on NSCLC:

- Cancer Research UK. Lung Cancer - Stage 3 https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-3.
- Cancer Research UK. Lung Cancer - Stage 4 https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-4
- Cancer Research UK. Symptoms of advanced cancer https://www.cancerresearchuk.org/about-cancer/lung-cancer/advanced/symptoms
- Cancer Research UK. Survival for lung cancer 2021 https://www.cancerresearchuk.org/about-cancer/lung-cancer/survival.
- Cancer Research UK. Lung cancer survival statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Three
- Cancer Research UK. The twenty most common cancers https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero.
- Cancer Research UK. Treatment options for non-small cell lung cancer (NSCLC). https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer
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- Macmillan Cancer Support. Non-small cell lung cancer (NSCLC). https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/non-small-cell-lung-cancer
- National Lung Cancer Audit. State of the Nation Report 2023: Results of the National Lung Cancer Audit for patients in England during 2021 and Wales during 2020–2021 https://www.lungcanceraudit.org.uk/content/uploads/2023/04/NLCA-State-of-the-Nation-2023-Version-2-amended-July-2023.pdf.
- Royal College of Physicians. National Lung Cancer Audit https://www.rcplondon.ac.uk/projects/national-lung-cancer-audit

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in

Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Alanine aminotransferase increased	Alanine aminotransferase (ALT) is a protein found in the blood. ALT is a measure of liver health. A high level of ALT in the blood is a sign that that the liver has been damaged.
Arthralgia	Joint pain.
Aspartate transferase increased	Aspartate transferase (AST) is a protein found in organs of the body such as the liver, heart, brain, pancreas and kidneys, as well as in tissues such as muscles. Increased amounts of AST in these organs or tissues indicates that they have been damaged.
Biomarker	A biological indicator, such as a gene, a protein or a molecule, which indicates a specific disease or process.
Biopsy	A medical procedure which involves taking a small sample of body tissue so it can be examined under a microscope.
Blood creatinine increased	Creatinine is a chemical waste product formed in the muscles when energy is released. Healthy kidneys remove creatinine from the blood. High levels of creatinine in the blood suggests that the kidneys are damaged.

Chemotherapy	A type of cancer therapy that uses drugs to kill cancer cells.
Clinical practice	The process of monitoring, diagnosing and treating patients' psychological and physical conditions. In the United Kingdom, this refers to healthcare services carried out by nurses, doctors and other healthcare professionals.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Computerised tomography (CT) scan	A procedure that uses a computer and an **X-ray** machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly.
Dyspnoea	Shortness of breath.
Electrocardiogram (ECG)	A medical device which measures electrical activity of the heart in order to monitor heart health and detect heart problems.
ECG QT prolongation	Long QT syndrome is an inherited heart problem that affects how the heart beats. In some people, this can cause fits (seizures) and/or fainting. An electrocardiogram (ECG) is a test which is often used to diagnose the condition.

Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
Fatigue	The feeling of having a lack of energy.
First-line	The first treatment a patient receives after being diagnosed with a condition.
Fusions	Fusions are a type of **genetic alteration** which can cause cancer if cells with these alterations are not repaired or removed from the body and instead multiply out of control.
Gene	A gene is an inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Genetic alterations	Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic alterations, which may be **mutations** or **fusions**. It is usual for cells to repair faults in their **genes** or for the faults to be removed by the body. Cancer happens when cells with genetic alterations are not repaired or removed from the body and instead multiply out of control.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**.
Histology	The microscopic structure of cells and tissues as seen under a microscope.
Hypertension	Also known as high blood pressure. This is caused by high pressure of blood in the **arteries**, the blood vessels that carry blood from the heart.

Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immunotherapy	A type of cancer therapy that uses the body's own **immune system** to kill cancer.
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Intravenous	This is when you are given medicine through an injection or drip (see '**intravenous drip**') into one of your veins.
Intravenous drip	Some cancer drugs are diluted in a bag of fluid which is connected to a very thin tube and goes into one of your veins.
Magnetic resonance imaging (MRI) scan	A procedure where a machine uses strong magnetic fields to produce images of structures inside the body.
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom.
Microscope	A piece of scientific equipment used for viewing very small objects, such as cells, which cannot be seen by the naked eye.

Mutations	Mutations are a type of **genetic alteration** which can cause cancer if cells with these alterations are not repaired or removed from the body and instead multiply out of control.
Next generation sequencing (NGS)	A technique where the sequence of genetic material inside cells is read to identify if there are any abnormal genes which could be driving cancer.
Non-small cell lung cancer (NSCLC)	Non-small cell lung cancer is a group of lung cancers named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are adenocarcinoma (most common), squamous cell carcinoma, and large cell carcinoma. Non-small cell lung cancer is the most common of the two main types of lung cancer (non-small cell lung cancer and small cell lung cancer).
Oedema	Swelling caused due to excess fluid accumulation in the body tissues. Oedema can occur in any part of the body.
Off-target effects	When a drug affects another pathway in the body in addition to the intended target. This can result in more numerous or severe side effects of treatment.
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works. Also called overall survival.
Phase I clinical trial	This type of **clinical trial** whereby healthy volunteers are given increasingly larger

	doses of a drug to determine the optimal dose for maximising the effectiveness of the drug, whilst also minimising **side effects**.
Phase II clinical trial	This type of **clinical trial** whereby patients with the condition of interest are given the drug to determine whether the drug is effective and safe.
Prognosis	This gives an idea about whether the cancer can be cured and what may happen in the future.
Programmed death ligand 1 (PD-L1)	PD-L1 is a protein on the surface of cells which suppresses the **immune system**. PD-L1 over activity is often linked to cancer, as PD-L1 on cancer cells prevents the immune system from becoming activated and able to kill the cancer cells.
Progression-free survival (PFS)	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year

	of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Radiotherapy	A type of cancer therapy that uses radiations to kill cancer cells.
Rearranged during transfection (RET)	RET is a **protein** encoded by the *RET* **gene**. The RET protein plays a role in normal development of tissues. **Mutation** or **fusions** of the *RET* gene can result in overactivity of the RET protein. This causes cells to multiple uncontrollably, leading to the development of cancer.
Regulatory bodies	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
***RET* fusion-positive**	Rearranged during transfection (*RET*) fusion-positive is a mutated **gene** which can cause cancer
Second-line	The second treatment a patient receives after being diagnosed with a condition.
Serum	A protein-rich liquid which is left over after the clotting of blood.
Serum electrolytes	Electrically charged particles which are found in the **serum** of the blood. These particles are essential for normal and healthy functioning of the body.

Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Targeted treatment	Targeted cancer drugs work by 'targeting' the differences between a cancer cell and normal cell that help cancer cells survive and grow. As these therapies target cancer cells specifically, they are more effective than conventional chemotherapy and they limit damage to healthy parts of the body.
Tumour	A lump of abnormal cells which develops as a result of the abnormal cells growing faster than normal, healthy cells.
Tumour response	The extent to which a **tumour** shrinks in response to treatment.
Tolerated	How a patient withstands any **side effects** of treatment.
X-ray	A diagnostic test which uses invisible energy beams to produce images of internal structures of the body.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (MA review of TA760) [ID6293]

Clarification questions

May 2024

File name	Version	Contains confidential information?	Date
ID6293_Selpercatinib in 2L RET fusion-positive NSCLC_Clarification Question Responses_[CON]	V1.0	**Yes**	23rd May 2024

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Additional analyses

A1. Priority question. The company has conducted network meta-analyses for a large network of evidence which includes studies of many irrelevant comparators; the inclusion of these studies is likely to substantially increase heterogeneity across the network. To explore the robustness of the company's indirect clinical effectiveness results, please conduct unanchored MAICs including LIBRETTO-001 trial IAS population data versus LUME-Lung 1 trial adenocarcinoma population data for the comparison of selpercatinib versus placebo+docetaxel and for the comparison of selpercatinib versus nintedanib+docetaxel.

Please provide MAIC results for the following outcomes:

- **ORR by IRC**
- **PFS by IRC**
- **OS**

For PFS by IRC and OS, please include an assessment of proportional hazards for:

- **adjusted LIBRETTO-001 trial selpercatinib data and LUME-Lung 1 trial placebo+docetaxel data and**
- **adjusted LIBRETTO-001 trial selpercatinib data and LUME-Lung 1 trial nintedanib+docetaxel data**

The EAG is aware that the MAIC treatment effects will be estimated for the LUME-Lung 1 trial adenocarcinoma population rather than for the LIBRETTO-001 trial IAS population.

Lilly have conducted unanchored matching-adjusted indirect comparisons (MAICs) for the LIBRETTO-001 trial integrated analysis set (IAS) data versus LUME-Lung 1 trial adenocarcinoma population data. These analyses were conducted for the comparison of selpercatinib versus docetaxel chemotherapy with placebo and for the comparison of selpercatinib versus docetaxel chemotherapy with nintedanib.

MAIC results

The hazard ratios resulting from these unanchored MAICs are presented alongside the equivalent hazard ratios from the CS in Table 1 (progression-free survival [PFS] by independent review committee [IRC]) and Table 2 (overall survival [OS]). These results demonstrate that the unanchored MAICs produce lower hazard ratios for selpercatinib versus both comparators than the indirect treatment comparison (ITC) approach taken in the CS. This is in line with the objective response rate (ORR) odds ratios presented in Table 3. Together, these data show that the ITC approach taken in the CS is conservative with respect to estimating the relative treatment effect selpercatinib versus both relevant comparators.

Table 1: Relative treatment effect estimates for selpercatinib versus comparators for PFS by IRC

Treatment	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median HR (95% CI)	RE model with informative priors, pairwise median HR (95% CrI)
Docetaxel monotherapy	[redacted]	[redacted]
Nintedanib plus docetaxel	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CrI: credible interval; HR: hazard ratio; IRC: independent review committee; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression free survival; RE: random effects.

Table 2: Relative treatment effect estimates for selpercatinib versus comparators for OS

Treatment	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median HR (95% CI)	RE model with informative priors, pairwise median HR (95% CrI)
Docetaxel monotherapy	[redacted]	[redacted]
Nintedanib plus docetaxel	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CrI: credible interval; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; RE: random effects.

Table 3: Relative treatment effect estimates for selpercatinib versus comparators for ORR

Treatment	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median OR (95% CI)	RE model with informative priors, pairwise median OR (95% CrI)
Docetaxel monotherapy	[redacted]	[redacted]
Nintedanib plus docetaxel	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CrI: credible interval; MAIC: matching-adjusted indirect comparison; OR: odds ratio; ORR: objective response rate; RE: random effects.

Assessment of proportional hazards for PFS by IRC and OS

The MAICs utilised to inform this response are dependent on the proportional hazards assumption, so this assumption was assessed for PFS by IRC and OS. Data assessed comprised:

- Docetaxel monotherapy: Adjusted LIBRETTO-001 trial data for selpercatinib versus LUME-Lung 1 trial data for docetaxel chemotherapy with placebo

- Nintedanib plus docetaxel: Adjusted LIBRETTO-001 trial data for selpercatinib versus LUME-Lung 1 trial data for docetaxel chemotherapy with nintedanib

The Schoenfeld residual plots over time for PFS by IRC and OS are presented in Figure 1 and Figure 2, respectively, for selpercatinib versus docetaxel monotherapy, and in Figure 3 and Figure 4, respectively, for selpercatinib versus nintedanib plus docetaxel. The log cumulative hazard plots for PFS by IRC and OS are presented in Figure 5 and Figure 6, respectively, for selpercatinib versus docetaxel monotherapy, and in Figure 7 and Figure 8, respectively, for selpercatinib versus nintedanib plus docetaxel. Results of the proportional hazard assessment are presented in Table 4 for PFS by IRC and in Table 5 for OS.

Regarding PFS, the Schoenfeld residual plots show that the estimate of hazard ratio over time (represented by the solid blue line) remains relatively stable over time versus both comparisons (Figure 1 and Figure 2), and the hazards associated with selpercatinib and each comparator do not cross and are relatively parallel, particularly after approximately Month 2 (Figure 5 and Figure 6). These results suggest the proportional hazards assumption holds for the PFS analyses. This conclusion is supported by the results of the proportional hazards assessment (Table 4), which were non-significant versus both comparisons (p=[redacted] and p=[redacted] for selpercatinib versus docetaxel monotherapy and selpercatinib versus nintedanib plus docetaxel, respectively).

For OS, the Schoenfeld residual plots show more variability in the estimate of hazard ratio over time versus both comparators (Figure 3 and Figure 4), but the hazards associated with selpercatinib and each comparator remain relatively parallel, particularly after approximately Month 2 (Figure 7 and Figure 8). The results of the proportional hazards assessment (Table 5) were significant for the selpercatinib versus docetaxel monotherapy analysis (p=[redacted]) but not for the selpercatinib versus nintedanib plus docetaxel analysis (p=[redacted]). Based on these results, there is evidence that the assumption of proportional hazards may not hold in the selpercatinib versus docetaxel monotherapy OS analysis. The PFS analyses showed no clear violation of the assumption of proportional hazards.

Figure 1: Schoenfeld residual plot over time (PFS by IRC, selpercatinib versus docetaxel monotherapy)

Abbreviations: IRC: Independent Review Committee; PFS: progression-free survival; TRT: treatment.

Figure 2: Schoenfeld residual plot over time (PFS by IRC, selpercatinib versus nintedanib plus docetaxel)

Abbreviations: IRC: Independent Review Committee; PFS: progression-free survival; TRT: treatment.

Figure 3: Schoenfeld residual plot over time (OS, selpercatinib versus docetaxel monotherapy)

Abbreviations: OS: progression-free survival; TRT: treatment.

Figure 4: Schoenfeld residual plot over time (OS, selpercatinib versus nintedanib plus docetaxel)

Abbreviations: OS: progression-free survival; TRT: treatment.

Figure 5: Log cumulative hazard plot (PFS by IRC, selpercatinib versus docetaxel monotherapy)

Abbreviations: IRC: Independent Review Committee; PFS: progression-free survival.

Figure 6: Log cumulative hazard plot (PFS by IRC, selpercatinib versus nintedanib plus docetaxel)

Abbreviations: IRC: Independent Review Committee; PFS: progression-free survival.

Figure 7: Log cumulative hazard plot (OS, selpercatinib versus docetaxel monotherapy)

Abbreviations: IRC: Independent Review Committee; OS: overall survival.

Figure 8: Log cumulative hazard plot (OS, selpercatinib versus nintedanib plus docetaxel)

Abbreviations: IRC: Independent Review Committee; OS: overall survival.

Table 4: Proportional hazard assessment for PFS by IRC, unanchored MAIC

Treatment	Chi square	Degrees of freedom	p value
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]

Abbreviations: IRC: Independent Review Committee; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival.

Table 5: Proportional hazard assessment for OS, unanchored MAIC

Treatment	Chi square	Degrees of freedom	p value
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]
Nintedanib plus docetaxel	[redacted]	[redacted]	[redacted]

Abbreviations: MAIC: matching-adjusted indirect comparison; OS: overall survival.

LIBRETTO-001 trial

A2. Please clarify whether all the efficacy and safety evidence presented in the CS is from phase II of the LIBRETTO-001 trial.

The clinical data informing the company submission are sourced from the January 2023 data cut-off of the LIBRETTO-001 trial.[1] At the specified data cut-off, the Phase I portion of the study is complete. Therefore, while patients included in datasets relevant to the company submission may have originated in the Phase I portion of the study (dose escalation and expansion), all data provided in the company submission are associated with the most recent data cut-off of the Phase II portion of LIBRETTO-001. Selpercatinib dosing in Phase II of LIBRETTO-001 was in line with the recommendations of the summary of product characteristics (SmPC).[2]

A3. Median PFS and OS follow-up are reported in the CS (CS, Table 5). Please provide the median follow-up for the primary outcome of ORR and please clarify the median follow-up times for the other secondary outcomes presented in the CS, including CNS ORR and DOR, AEs and EORTC QLQ-C30.

The median follow-up data for the specified outcomes for the IAS patient population in the LIBRETTO-001 trial are presented in Table 6.

Table 6: Duration of follow-up for treatment-exposed *RET* fusion-positive NSCLC patients (IAS)

Outcome	Median follow-up in IAS (treatment-exposed; N=247), months
ORR	[redacted]
CNS ORR and DOR[a]	25.8
Adverse events	[redacted]
EORTC QLQ-C30	[redacted]

[a] For CNS-related outcomes, data are given for the NSCLC CNS cohort (n=[redacted]).
Abbreviations: CNS: central nervous system; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; DOR: duration of response; IAS: integrated analysis set; NSCLC: non-small cell lung cancer; ORR: objective response rate; RET: rearranged during transfection.

A4. Please provide data on the type of prior cancer-related systemic treatments (platinum chemotherapy, anti-PD-L1 therapy, MKIs) received by the LIBRETTO-001 trial RET fusion-positive NSCLC IAS population.

The prior cancer-related systemic treatments received by the LIBRETTO-001 trial *RET* fusion-positive NSCLC IAS patient population are detailed in Table 7 below.

Table 7: Prior cancer-related systemic treatments for treatment-exposed *RET* fusion-positive NSCLC patients (IAS)

Type of prior systemic therapy,[a] n (%)	IAS (treatment-exposed), N=247
Chemotherapy	[redacted]
Platinum	[redacted]
Taxane	[redacted]

Immunotherapy	[redacted]
Anti-PD-1/PD-L1 therapy	[redacted]
Anti-CTLA4 therapy	[redacted]
Multikinase inhibitor	[redacted]
Cabozantinib	[redacted]
Vandetanib	[redacted]
Sorafenib	[redacted]
Lenvatinib	[redacted]
Other MKIs	[redacted]
Other	[redacted]
VEGF/VEGFR inhibitor	[redacted]
EGFR inhibitor	[redacted]
Selective RET inhibitor	[redacted]
mTOR inhibitor	[redacted]
RAI	[redacted]
Hormonal therapy	[redacted]

Abbreviations: CTLA4: cytotoxic T-lymphocyte-associated protein 4; EGFR: estimated glomerular filtration rate; IAS: integrated analysis set; MKI: multikinase inhibitor; mTOR: mechanistic target of rapamycin; NSCLC: non-small cell lung cancer; PD-1: programmed cell death 1 receptor; PD-L1: programmed cell death receptor ligand 1; RAI: radioactive iodine; RET: rearranged during transfection; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 cut-off).[1] Table 1.4.

A5. It is stated in the CS (p53) that [redacted] patients in the LIBRETTO-001 trial NSCLC IAS trial population responded to treatment with selpercatinib, and also that, "As of the 13th January 2023 data cut-off, [redacted] patients had maintained a response for ≥12 months in the IAS population." Please clarify how [redacted] patients maintained a response for ≥12 months when only [redacted] patients responded to treatment?

Lilly apologise for this inconsistency in reporting and can confirm that the number of patients in the IAS population who responded to treatment was [redacted]. The observed number of patients maintaining a response for ≥12 months was [redacted].

Selpercatinib versus docetaxel pseudo-comparator arm

A6. Please clarify whether the company's estimation of treatment effects (CS, Table 20) for selpercatinib versus placebo+docetaxel (pseudo-control arm) were adjusted for differences between the LIBRETTO-001 trial IAS population and the REVEL trial placebo+docetaxel arm (non-squamous population) baseline characteristics that remained following the propensity score matching (CS, Table 19). If adjustments were made, please provide details of how adjustments were performed. If no

adjustments were made, please explain how these imbalances may have impacted the company's indirect clinical effectiveness results.

As detailed in the CS, differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the docetaxel chemotherapy plus placebo arm from REVEL were adjusted for using propensity score matching. The prognostic variables used in this propensity score matching were validated by a UK expert clinician as being clinically relevant factors for adjustment, and this is in line with the conclusions of the NICE Committee in the previous appraisal of selpercatinib in this indication.[3, 4] In order to have data that allowed for matching, [redacted] patients from the LIBRETTO-001 dataset were excluded from the analysis: 7 had ECOG PS 2 at baseline, [redacted] patients did not have non-squamous disease, and [redacted] patients with missing race data, resulting in a population of [redacted] patients matched to patients in the REVEL trial.

Patient baseline characteristics and the standardised mean difference between these characteristics before and after propensity score matching of REVEL to LIBRETTO-001 trial data are presented in Table 8, which is an extended version of Table 19 presented in Document B of the Company Submission (CS). Given that these data demonstrate that propensity score matching resulted in similar patient baseline characteristics between trials, no further adjustments were made following this matching process, and the results of the ITC are not anticipated to be materially impacted by any minor remaining differences.

Table 8: Summary of patient characteristics of the REVEL and LIBRETTO-001 trial populations – extended

Characteristic	Baseline characteristics				
	LIBRETTO-001 (selpercatinib; N=[redacted])	Before PSM		After PSM[a]	
		REVEL (docetaxel + placebo; N=447)	Std mean difference	REVEL (docetaxel + placebo; N=234)	Std mean difference
Age (mean, years)	[redacted]	59.82	–0.07	59.00	0.00
ECOG PS = 1, %	[redacted]	68.3%	–0.12	61.5%	0.02
Female, %	[redacted]	38.4%	0.37	46.2%	0.21
Never smoked, %	[redacted]	25.9%	0.89	48.3%	0.40
Race: Asian, %	[redacted]	14.2%	0.78	26.1%	0.50
Race: Other[b], %	[redacted]	6.7%	0.04	11.1%	–0.13
Stage III, %	[redacted]	8.9%	–0.11	6.4%	–0.02
Stage IV, %	[redacted]	86%	0.19	91.9%	0.00
Time since diagnosis to start of trial, median months	[redacted]	12.04	0.92	15.12	0.79

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

A7. Please provide the ORR results that were generated for the comparison of selpercatinib versus the placebo+docetaxel pseudo-control arm (and subsequently included in the company ORR NMA).

The ORR odds ratio generated for the comparison of selpercatinib versus the docetaxel chemotherapy with placebo pseudo-control arm is presented in Table 9.

Table 9: ORR odds ratio for selpercatinib versus docetaxel chemotherapy with placebo (pseudo-control arm)

Treatment	OR (95% CrI)
Selpercatinib versus docetaxel chemotherapy with placebo	[redacted]

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

A8. Please provide the following REVEL trial placebo+docetaxel arm (non-squamous population) baseline characteristics:

- RET fusion status
- presence of brain metastases

Data on RET fusion status were not collected as part of the REVEL trial so are not available for presentation.

The proportions of patients with brain metastases at baseline in the LIBRETTO-001 (IAS) and REVEL trials are presented in Table 10; a considerably larger proportion of patients had brain metastases at baseline in the IAS population of the LIBRETTO-001 trial than in the REVEL trial, and no adjustment was specifically made for this in the indirect comparison. However, adjustment was made for the proportion of patients with Stage IV (metastatic) disease, which would have accounted for metastases more broadly, including brain metastases.

In addition, given that the presence of brain metastases is well-established as a negative prognostic factor in NSCLC,[5, 6] if lack of adjustment for brain metastases at baseline were to impact results, it is anticipated that this will have biased the efficacy estimates generated by the NMA towards the pseudo-control arm. This is supported by the results of a subgroup analysis presented in Document B of the CS that assessed median duration of IRC-assessed PFS in patients with CNS metastases (n=[redacted]). Median duration of PFS by IRC in this sub-population was [redacted] months (95% CI: [redacted]) as compared to 26.15 months (95% CI: 19.3–35.7) in the overall IAS population (N=247).

Table 10: Proportion of patients with brain metastases at baseline

	Proportion of patients, n/N (%)
LIBRETTO-001 (IAS)	77/247 (31.2)
REVEL	24/625 (3.8)

Abbreviations: IAS: integrated analysis set.

Network-meta analyses

A9. Please clarify whether the trial PFS and ORR outcome data used in the company NMAs were assessed by IRC or by investigator? Please also confirm that, for all trials that provided data used in the NMAs, data were extracted from the most up to date sources.

The trial PFS and ORR outcome data used in the company NMAs were consistently assessed by Independent Review Committee (IRC). For all trials that informed the NMAs, data were extracted from the most up to date sources. As detailed in the CS appendices, the NMAs were informed by an SLR first initiated in September 2019. Subsequent updates to this SLR, the most recent of which was in January 2024, ensured that trial data included in the NMAs were the most up to date available.

A10. Regarding the assessment of between trial heterogeneity, it is stated in the CS (p72) that the only model to converge for OS and PFS was age. However, on CS, p73 it is stated that, “The majority of baseline characteristics were not identified as significant suggesting the impact of any between-trial heterogeneity on the model results would be minimal.” How is it possible to reach this conclusion if age was the only baseline characteristic to converge, precluding meta-regression for the other baseline characteristics?

As stated in Section B.2.9.4 of Document B of the CS, patient age was the only baseline characteristic for which the PFS and OS models both converged; the year of study publication converged for OS only. In cases where insufficient aggregate data were available to permit model convergence, conclusion of statistical significance or statistical non-significance of that baseline characteristic on model results is not possible. As such, Lilly maintain that the majority of baseline characteristics were not identified to be significant, but acknowledge that the impact of between-trial heterogeneity in characteristics that did not converge is undetermined.

Section B: Clarification on cost effectiveness data

B1. Priority question. Please clarify whether IRC-assessed or investigator-assessed selpercatinib PFS data were used in the company model.

Lilly can confirm that IRC-assessed selpercatinib PFS data, a pre-specified secondary endpoint of the LIBRETTO-001 study, were used in the company model.

B2. Priority question. Were curves fitted to LIBRETTO-001 trial unadjusted or adjusted PFS, OS and TTD data? If the data were adjusted, please describe the

approach(es) used to adjust these data and also provide plots showing unadjusted and adjusted data.

The extrapolation curves for selpercatinib PFS and OS in the economic model were fitted to data adjusted via PSM (see Clarification Question A6 above, and Section B.2.9.1 of CS Document B for full details). The Kaplan-Meier charts pre- and post-matching are presented below for PFS (Figure 9 and Figure 10, respectively) and OS (Figure 11 and Figure 12, respectively).

Figure 9: Kaplan-Meier charts for PFS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients before propensity score matching

Abbreviations: NSCLC: non-small cell lung cancer; PFS: progression free survival; RET: rearranged during transfection.

Figure 10: Kaplan-Meier charts for PFS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients following propensity score matching (updated Figure 9 in CS Document B)

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

Figure 11: Kaplan-Meier charts for OS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients before propensity score matching

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival; RET: rearranged during transfection.

Figure 12: Kaplan-Meier charts for OS for selpercatinib and docetaxel chemotherapy plus placebo pseudo-control arm in previously treated NSCLC patients following propensity score matching (updated Figure 9 in CS Document B)

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

B3. Priority question. Please repeat the company base case cost effectiveness analyses using the outcomes from the MAICs requested in clarification question A1.

Lilly have conducted unanchored MAICs including the LIBRETTO-001 trial IAS population data versus LUME-Lung 1 trial adenocarcinoma population data for the comparison of selpercatinib versus docetaxel chemotherapy with placebo and docetaxel chemotherapy with nintedanib, respectively (see response to Clarification Question A1 above for full details).

As presented in response to Clarification Question A1 above, the unanchored MAICs produced consistently lower HRs for selpercatinib than those presented in the CS across both comparators and outcomes. Therefore, if used to inform the economic model, these results would result in a lower ICER for selpercatinib versus both comparators. However, Lilly maintain that the approach submitted in the CS in which patient level data from REVEL are used to establish a control arm is more methodologically robust than this unanchored MAIC analysis. For this reason, the company base case cost effectiveness analyses have not been updated to include the outcomes of these MAICs.

B4. Priority question. Please provide external validation of the docetaxel (pseudo-control arm) PFS and OS estimates, for example, by using Flatiron data.

As described in the CS, external validation of PFS and OS estimates associated with the docetaxel (pseudo-control arm) was provided by a UK clinical expert on NSCLC. The parametric

curves used for docetaxel chemotherapy (PFS: Spline Knot 3; OS: Exponential) were selected for use in the submitted economic model based on clinician input that these resulted in the most clinically plausible landmark and median survival estimates for the docetaxel chemotherapy pseudo-control arm.

Section C: Textual clarification and additional points

C1. Please provide the most recent versions of the LIBRETTO-001 trial protocol and SAP.

The most recent versions of the LIBRETTO-001 trial protocol and SAP, respectively, have been provided in the reference pack associated with this document.

C2. Please provide the latest versions of the clinical effectiveness and economic SLR protocols.

The most recent versions of the clinical and economic SLR protocols informing the company submission have been provided in the reference pack associated with this document.

C3. Please clarify whether all LIBRETTO-001 trial AE data reported in CS, Table 32 are correct. Specifically, please clarify whether the IAS population oedema and increased blood creatinine data are correct.

Lilly thank the EAG for noting that the proportion of patients in the IAS population who experienced increased blood creatinine (any grade) is incorrectly reported in the CS and can confirm that this should be [redacted]247 ([redacted]%), while the proportion experiencing this treatment-emergent adverse event (TEAE) at Grade ≥3 in the IAS population should be reported as ([redacted]247, [redacted]%).

Regarding the oedema data, the data reported in the CS correspond to the preferred term "oedema", which was correctly stated as [redacted]247 ([redacted]%) patients experiencing any grade and [redacted]247 ([redacted]%) patients experiencing Grade ≥3. For clarity, and in alignment with the data reported from the OSAS population, the proportion of patients who had oedema adverse events for all preferred terms applicable to any form of oedema are presented in Table 11. Note that patients may have been recorded to experience more than one oedema adverse event.

Table 11: Oedema adverse events in the IAS patient population (N=247)

Preferred term, n (%)	Any grade	Grade ≥3
Oedema peripheral	[redacted]	[redacted]
Face oedema	[redacted]	[redacted]
Periorbital oedema	[redacted]	[redacted]
Localised oedema	[redacted]	[redacted]
Generalised oedema	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]
Brain oedema	[redacted]	[redacted]
Lymphoedema	[redacted]	[redacted]
Oedema	[redacted]	[redacted]

Pulmonary oedema	[redacted]	[redacted]
Skin oedema	[redacted]	[redacted]
Vasogenic cerebral oedema	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]
Papilloedema	[redacted]	[redacted]
Retinal oedema	[redacted]	[redacted]
Oedema genital	[redacted]	[redacted]

Abbreviations: IAS: integrated analysis set.
Source: Eli Lilly and Company Ltd. Data on file.[7]

C4. The selpercatinib versus docetaxel NMA PFS results (CS, Table 23) and NMA OS results (CS, Table 25) are identical to the results for selpercatinib versus the docetaxel pseudo-control arm (CS, Table 20). Please confirm that the results presented in Table 23 and Table 25 are correct.

Lilly can confirm that the results presented in Table 23 and Table 25 of Document B of the CS are correct. However, an updated, corrected version of Table 20 of Document B of the CS, the estimated treatment effect for selpercatinib versus docetaxel chemotherapy plus placebo pseudo-control arm, is presented in Table 12.

Table 12: Estimated treatment effects for selpercatinib versus docetaxel chemotherapy plus placebo (pseudo-control arm)

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

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

C5. The EAG considers that the most recent clinical effectiveness search strategies (SLR4, January 2024) reported in the CS, Appendix D, Table 10 to 12 unclear. In particular:

- Table 10, #18: How was it possible to include searches for #18 to #22 (included as search terms in this command line) when, by definition, #18 and #19 to #22 refer to commands that had not yet been run? Similarly, lines #19, #22, #25, #28, #30, #31, #32 and #33 include search commands that had not yet been run.
- Table 11: Similar issues to those identified in Table 10 can be found in lines #18, #19, #22, #25, #28, #30, #31, #32 and #33.
- Table 12: The same issues to those identified in Table 10 and Table 11 can be found in lines #18, #19, #22, #25, #28, #30, #31, #32 and #33.

Please provide the correct search strategies for these updated searches.

Lilly can confirm this to be a reporting error. The correct search strategies for CS Appendix D Table 10, Table 11 and Table 12 are presented below in Table 13, Table 14 and Table 15, respectively. All changes from the previously presented tables in CS Appendix D are marked in **bold**.

Table 13: Embase search strategy for clinical trial evidence for selpercatinib and comparators in the second-line setting (conducted on 18th January 2024; SLR4) – revised CS Appendix D Table 10

Search number	Search Terms	Hits
1	exp lung neoplasms/	524,658
2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	154,758
3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	142,756
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	454,017
5	1 or 2 or 3 or 4	639,602
6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	1,752,924
7	5 and 6	224,380
8	(second line therapy or second-line or second line or 2nd line or relapse or relapsed or refractory or recurrent or resistant or failed or rescue or pretreated or pre-treated or previously treated or retreated or progressive).tw,kw.	2,840,868
9	7 and 8	42,824
10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	1382
11	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	77,580
12	(nintedanib or ofev or vargatef).mp.	6081
13	11 and 12	578
14	**(atezolizumab or mpdl3280a or mpdl 3280a or rg7446 or rg 7446 or tecentriq or tecntriq).mp.**	**17,441**
15	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	5225
16	**11 and 15**	**1266**
17	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch 900475).mp.	41,263
18	**(nivolumab or bms936558 or bms 936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.**	**41,634**
19	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	26,348

20	**(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.**	**7863**
21	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	5787
22	**(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.**	**33,907**
23	10 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 21 or 22	125,556
24	9 and 23	10,097
25	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	4,950,937
26	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	12,612,114
27	25 not 26	2,722,014
28	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	3,317,451
29	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	7,362,418
30	28 or 29	9,187,730
31	animal/ not (animal/ and human/)	1,627,744
32	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	12,975,040
33	31 or 32	14,397,617
34	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	5601
35	(9 and 34 and 30) not (27 or 33)	122
36	limit 35 to dc=20210713-20240118	64
37	(24 and 28) not (27 or 33)	2337
38	limit 37 to dc=20210713-20240118	375

Table 14: Medline search strategy for clinical trial evidence for selpercatinib and comparators in the second-line setting (conducted on 18th January 2024; SLR4) – revised CS Appendix D Table 11

Search number	Search Terms	Hits
1	exp lung neoplasms/	280,455
2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	90,224

3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	89,555
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	299,453
5	1 or 2 or 3 or 4	386,307
6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	1,155,655
7	5 and 6	118,053
8	(second line therapy or second-line or second line or 2nd line or relapse or relapsed or refractory or recurrent or resistant or failed or rescue or pretreated or pre-treated or previously treated or retreated or progressive).tw,kw.	1,921,640
9	7 and 8	18,497
10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	530
11	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	20,509
12	(nintedanib or ofev or vargatef).mp.	1746
13	11 and 12	88
14	**(atezolizumab or mpdl3280a or mpdl 3280a or rg7446 or rg 7446 or tecentriq or tecntriq).mp.**	**3420**
15	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	1323
16	**11 and 15**	**175**
17	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch 900475).mp.	9660
18	**(nivolumab or bms936558 or bms 936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.**	**10,252**
19	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	9926
20	**(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.**	**1730**
21	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	1113
22	**(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.**	**8220**
23	10 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 21 or 22	38,488
24	9 and 23	2930
25	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	4,599,491
26	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	9,072,376
27	25 not 26	2,315,016

28	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	2,360,723
29	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	1,495,131
30	28 or 29	3,284,262
31	animal/ not (animal/ and human/)	5,153,512
32	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	4,352,621
33	31 or 32	8,708,547
34	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	5323
35	(9 and 34 and 30) not (27 or 33)	35
36	limit 35 to dt=20210713-20240118	19
37	(24 and 28) not (27 or 33)	688
38	limit 37 to dt=20210713-20240118	88

Table 15: Evidence-Based Medicine Reviews for clinical trial evidence for selpercatinib and comparators in the second-line setting (conducted on 18th January 2024; SLR4) – revised CS Appendix D Table 12

Search number	Search Terms	Hits
1	exp lung neoplasms/	11,091
2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	16,934
3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	16,248
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	28,620
5	1 or 2 or 3 or 4	30,564
6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	112,056
7	5 and 6	15,501
8	(second line therapy or second-line or second line or 2nd line or relapse or relapsed or refractory or recurrent or resistant or failed or rescue or pretreated or pre-treated or previously treated or retreated or progressive).tw,kw.	207,444
9	7 and 8	4742

10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	49
11	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	8838
12	(nintedanib or ofev or vargatef).mp.	778
13	11 and 12	48
14	**(atezolizumab or mpdl3280a or mpdl 3280a or rg7446 or rg 7446 or tecentriq or tecntriq).mp.**	**1438**
15	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	689
16	**11 and 15**	**164**
17	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch 900475).mp.	3062
18	**(nivolumab or bms936558 or bms 936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.**	**2996**
19	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	3504
20	**(cabozantinib or bms 907351 or bms907351 or cabometyx or cabozantinib malate or cabozantinib s malate or cabozantinib smalate or cometriq or xl 184 or xl184).mp.**	**540**
21	(vandetanib or azd 6474 or azd6474 or caprelsa or vandetinib or zactima or zd 6474 or zd6474).mp.	268
22	**(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.**	**1941**
23	10 or 13 or 14 or 16 or 17 or 18 or 19 or 20 or 21 or 22	12,320
24	9 and 23	1973
25	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	344,328
26	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	1,103,540
27	25 not 26	146,799
28	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	1,569,107
29	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	756,940
30	28 or 29	1,650,270
31	animal/ not (animal/ and human/)	18
32	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	141,790
33	31 or 32	141,805
34	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c	100

	RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	
35	(9 and 34 and 30) not (27 or 33)	15
36	limit 35 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	5
37	(24 and 28) not (27 or 33)	1515
38	limit 37 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	275

C6. The company uses the term “95% credible intervals” when referring to the estimated treatment effect for selpercatinib versus placebo+docetaxel (pseudo-control arm). There is no reference in the CS (or accompanying appendices) to Bayesian methods having been used to generate treatment effect estimates for the comparison of selpercatinib versus placebo+docetaxel (pseudo-control arm). Should the text on p66 of the CS (and in CS, Table 20) refer to 95% confidence intervals rather than 95% credible intervals?

Given that the data in Table 20 of Document B of the CS refer to estimated treatment effect following propensity score matching, Lilly thank the EAG for highlighting that the correct terminology for use here is “95% confidence intervals”. However, Lilly note that the values in Table 20 of Document B of the CS subsequently informed the associated NMAs, which were conducted using Bayesian mixed-treatment comparisons as described in the NICE DSU TSD.[8] Therefore, estimated treatment effects resulting from the NMAs are associated with 95% credible intervals.

C7. Priority question. Please comment on the differences between PFS by IRC (CS, Table 16) and PFS by investigator (CS Appendix L, Table 45) including differences in censoring, median PFS and landmark PFS. Please justify the use of the relevant definition of PFS used in the indirect treatment comparison (see A9) and the economic model (see B1), particularly if different definitions of PFS are used in the NMA and model. Please comment on the potential impact of choosing to use one PFS definition over another in both the NMA and model.

IRC assessment and investigator (INV) assessment of clinical outcomes are two commonly used approaches leading to the generation of key clinical data. PFS results by IRC and by INV from the IAS population of the LIBRETTO-001 trial, including resulting differences in censoring, median PFS and landmark PFS, are presented in Table 16. These IRC and INV data have been

reproduced from the CS (Table 16 of Document B and Table 45 of the Appendices document, respectively).

IRC assessment reflects the opinion of a committee rather than an individual researcher as in INV assessment. Therefore, IRC assessment may be considered a more robust and accurate method of assessment than investigator-led assessment, with INV assessment being reported to result in higher variability in response rate outcomes than IRC assessment.[9] The results for both methods of assessment are presented in Table 16.

Table 16: PFS for treatment-exposed *RET* fusion-positive NSCLC patients (IAS; IRC and Investigator assessment)

	IAS (treatment-exposed; N=247) – IRC	IAS (treatment-exposed; N=247) – INV
Progression status, n (%)[a]		
Disease progression	[redacted]	[redacted]
Death (no disease progression beforehand)	[redacted]	[redacted]
Censored	114 (46.2)	[redacted]
Reason censored, n (%)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Died or documented PD after missing 2 or more consecutive visits	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS (months)[b,c]		
Median	26.15	[redacted]
95% CI	19.3, 35.7	[redacted]
Minimum-maximum	[redacted]	[redacted]
Rate (%) of PFS[b,d]		
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	41.1 (34.2–47.9)	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
≥60 months (95% CI)	[redacted]	[redacted]

[a] Status as of the patient's last disease assessment on or before 13th January 2023. [b] Estimated based on Kaplan-Meier method (+ = censored observation). [c]95% CI was calculated using Brookmeyer and Crowley method. [d]95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; IAS: integrated analysis set; INV: investigator-assessed; IRC: independent review committee; NSCLC: non-small cell lung cancer; PD: progressed disease; PFS: progression-free survival.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2023 (13th January 2023 data cut-off). Table JZJA.5.3.[1]

References

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer – data review

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

National Disease Registration Service
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NHS England

Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of selpercatinib for treating RET (rearranged during transfection) fusion-positive non-small-cell lung cancer (NSCLC). The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and treatment duration in the evidence submission. As a result, they recommended the commissioning of selpercatinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of selpercatinib in the CDF population, during the managed access period. This report presents the results of the use of selpercatinib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 96% of patients and 100% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for selpercatinib for treating RET fusion-positive NSCLC in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 25 November 2021 and 31 May 2023, 35 applications for selpercatinib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 24 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

24 /25 (96%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was not reached. 81% of patients were still receiving treatment at 6 months [95% CI: 58%, 93%].

At data cut off, 17% (N=4) of patients were identified as no longer being on treatment. Of these four patients:

- 50% (N=2) of patients stopped treatment due to progression of disease
- 25% (N=1) of patients stopped treatment due to acute toxicity
- 25% (N=1) of patients were treated palliatively and did benefit from the treatment they received

The median OS was not reached. OS at 6 months was 96% [95% CI: 73%, 99%] and OS at 12 months was 91% [95% CI: 67%, 98%].

Conclusion

This report analysed SACT real-world data for patients treated with selpercatinib for the treatment of RET fusion-positive NSCLC in the CDF. It evaluated treatment duration, OS and treatment outcomes for all patients treated with selpercatinib for this indication.

Introduction

Lung cancer (ICD-10: C33 and C34) accounts for 12% of all cancer diagnoses in England. In 2021, 39,635 patients were diagnosed with lung cancer (males 20,312, females 19,323)[2].

- selpercatinib is recommended for use within the Cancer Drugs Fund as an option for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults who need systemic therapy after immunotherapy, platinum-based chemotherapy or both.

It is recommended only if the conditions in the managed access agreement for selpercatinib are followed[3].

2. Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (NSCLC) [TA760]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of selpercatinib (Eli Lilly and Company Limited) in treating RET fusion-positive NSCLC [TA760] and published guidance for this indication in January 2022[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of selpercatinib for the treatment of RET fusion-positive NSCLC through the CDF for a period of 29 months, from November 2021 to April 2024. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from an ongoing clinical trial (LIBRETTO-001[7]) evaluating selpercatinib in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the LIBRETTO-001 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for selpercatinib for the treatment of RET fusion-positive NSCLC in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the LIBRETTO-001 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- the prognostic effect, if any, of the RET fusion mutation
- immaturity of the progression-free and overall survival in people who have had selpercatinib
- immaturity of time to discontinuation (TTD) data

NHS England have calculated overall survival and treatment duration. Progression free survival will be included in the LIBRETTO-001 trial results.

Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (Eli Lilly and Company Limited) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA sets out the real-world data to be collected and analysed to support the NICE re-appraisal of selpercatinib. It also detailed the eligibility criteria for patient access to selpercatinib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for selpercatinib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3. Methods

CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS England, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Selpercatinib clinical treatment criteria

- application for selpercatinib is being made by and the first cycle of systemic anti-cancer therapy with selpercatinib will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- patient has locally advanced or metastatic non-small cell lung cancer
- patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer
- patient's NSCLC has been shown to harbour a RET gene fusion as determined on a tumour tissue biopsy or a plasma specimen (liquid biopsy) or both
- patient's RET fusion partner has been determined to be in one of these categories: KIF5B, CCDC6, NCOA4, RELCH, another fusion partner, unknown fusion partner
- patient has previously received immunotherapy and/or platinum-based chemotherapy for this locally advanced or metastatic NSCLC indication
- patient has not previously received selpercatinib or any other TKI which targets the RET receptor unless the patient has received selpercatinib via a company early access scheme and the patient meets all the other criteria listed here
- patient has an ECOG performance status (PS) score of 0 or 1 or 2
- patient either has no known brain metastases or if the patient does have brain metastases, then the patient is symptomatically stable before staring selpercatinib
- selpercatinib will be used as monotherapy
- clinician is aware of the following issues as regards the administration of selpercatinib as detailed in its Summary of Product Characteristics (SPC):
    - the dosage of selpercatinib is according to body weight
    - selpercatinib has reduced solubility at a higher pH and hence precautions are necessary with the co-administration of proton pump inhibitors or H2 antagonists
    - selpercatinib has clinically important interactions with CYP3A inhibitors or CYP3A inducers
- patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment whichever is the sooner
- a formal medical review as to how selpercatinib is being tolerated and whether treatment with selpercatinib should continue or not will be scheduled to occur at least by the start of the third 4-weekly cycle of treatment
- when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, clinician will complete a treatment break approval form to restart treatment, including as appropriate if the patient has had an extended break on account of Covid-19
- selpercatinib is to be otherwise used as set out in its Summary of Product Characteristics (SPC)

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for selpercatinib for the treatment of RET fusion-positive NSCLC for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for selpercatinib for the treatment of RET fusion-positive NSCLC for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for selpercatinib for the treatment of RET fusion-positive NSCLC and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

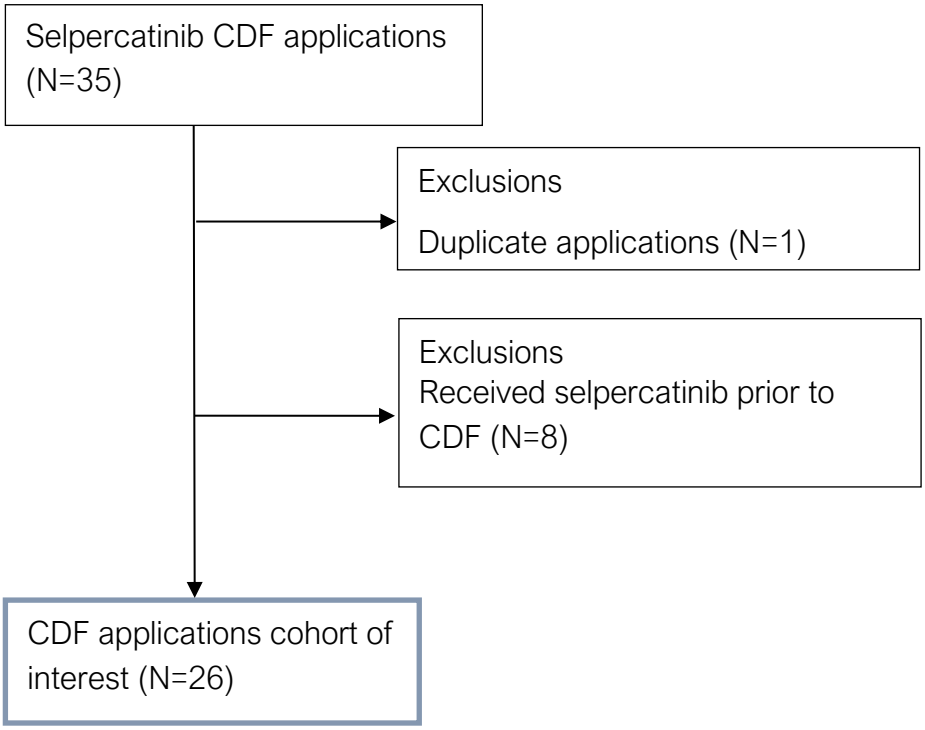
Initial CDF cohorts

The analysis cohort is limited to the date selpercatinib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 25 November 2021 to 31 May 2023. A snapshot of SACT data was taken on 2 September 2023 and made available for analysis on 11 September 2023 and includes SACT activity up to 31 May 2023. Tracing the patients' vital status was carried out on 28 September 2023 using the Personal Demographics Service (PDS)[1].

There were 35 applications for CDF funding for selpercatinib for the treatment of RET fusion-positive NSCLC between 25 November 2021 and 31 May 2023 in the NHS England Blueteq database. Following de-duplication this relates to 34 unique patients. Eight patients were excluded as they received selpercatinib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for selpercatinib for the treatment of RET fusion-positive NSCLC between 25 November 2021 and 31 May 2023



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for selpercatinib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week

cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Selpercatinib is administered orally. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Selpercatinib is a 28-day cycle consisting of one administration of 28 tablets[9].

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patient's date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

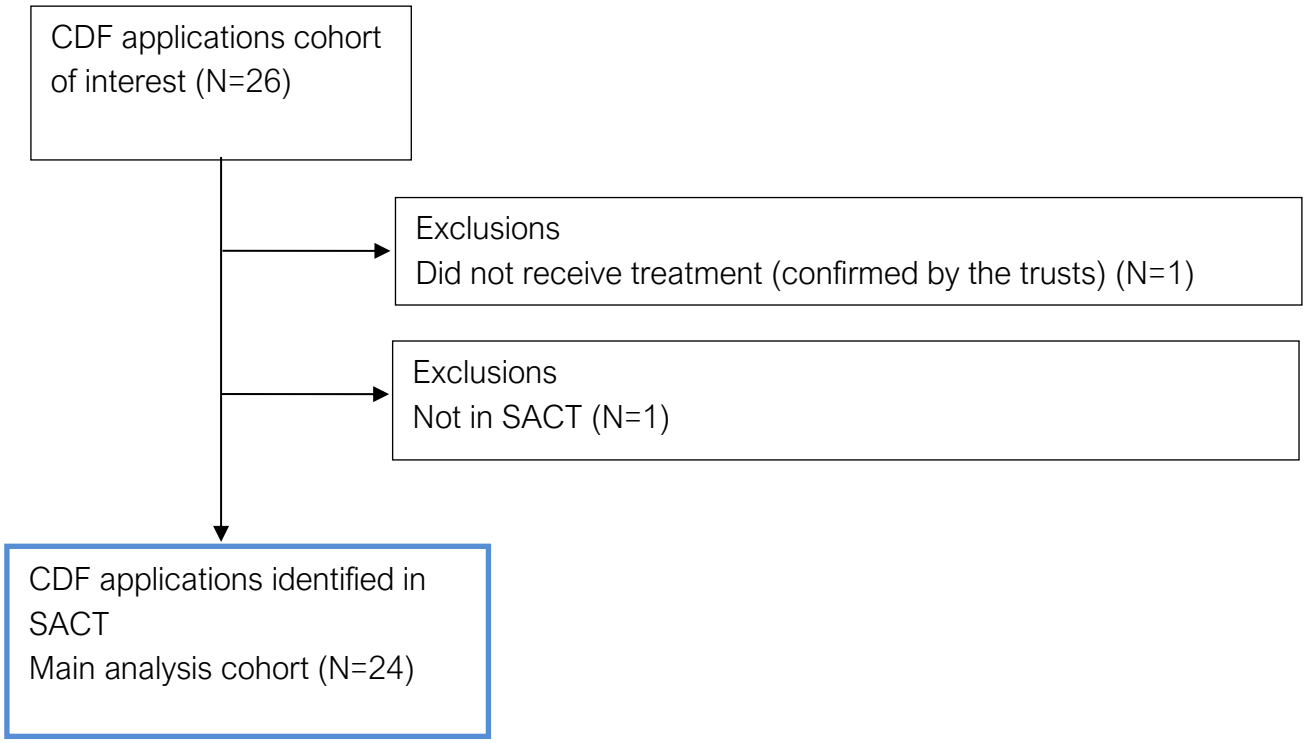
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4. Results

Cohort of interest

Of the 26 applications for CDF funding for selpercatinib for the treatment of RET fusion-positive NSCLC, one patient did not receive treatment and one patient was missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for selpercatinib for the treatment of RET fusion-positive NSCLC between 25 November 2021 and 31 May 2023



A maximum of 25 selpercatinib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 96% (24/25) of these applicants for CDF funding have a treatment record in SACT.

[a] The patients who did not receive treatment was confirmed by the relevant trust.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness was 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen was 67% complete.

Table 1: Completeness of key SACT data items for the selpercatinib cohort (N=24)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	67%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with selpercatinib in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for four patients. Of these, all patients (100%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=4)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	100%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. All Blueteq data items are 100% complete.

Table 3: Completeness of Blueteq key variables (N=24)

Variable	Completeness (%)
Histologically or cytologically confirmed diagnosis of NSCLC	100%
Type of specimen	100%
RET fusion partner category	100%
Previous immunotherapy/platinum-based chemotherapy for NSCLC	100%
Brain/Central Nervous System (CNS) metastases	100%

Patient characteristics

The median age of the 24 patients receiving selpercatinib for the treatment of RET fusion-positive NSCLC was 63.5 years. The median age in males and females was 61 and 66 years respectively.

Table 4: Patient characteristics (N=24)

Patient characteristics[b]			
		N	%
Gender	Male	9	38%
	Female	15	63%
Age	<40	1	4%
	40 to 49	3	13%
	50 to 59	6	25%
	60 to 69	7	29%
	70 to 79	5	21%
	80+	2	8%
Performance status at the start of regimen	0	4	17%
	1	10	42%
	2	2	8%
	3	0	0%
	4	0	0%
	Missing	8	33%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items with all 24 patients being treated for non-squamous NSCLC. The biopsy specimen was a tumour biopsy in 83% (N=20) of patients and a plasma specimen in 17% (N=4) of patients.

A patients RET fusion partner was determined to be KIF5B in 46% (N=11) of patients, 29% (N=7) of patients had an unknown RET fusion partner, 13% (N=3) of patients had a CCDC6, 8% (N=2) of patients had another RET fusion partner and 4% (N=1) of patients had a NCOA4.

71% (N=17) of patients received 1st line combination treatment of platinum-based chemotherapy with immunotherapy with or without 2nd line cytotoxic chemotherapy, 17% (N=4) of patients received 1st line platinum based cytotoxic chemotherapy with or without 2nd line cytotoxic chemotherapy, 4% (N=1) of patients received 1st line platinum based cytotoxic chemotherapy followed by 2nd line immunotherapy monotherapy, 4% (N=1) of patients received 1st line immunotherapy monotherapy only and 4% (N=1) of patients received 1st line platinum-based cytotoxic chemotherapy only.

Brain/CNS metastases was found in 16% (N=4) of patients.

Table 5: Distribution of key Blueteq data items (N=24)

Blueteq data items[c]		N	%
Histologically or cytologically confirmed diagnosis of NSCLC	Non squamous NSCLC	24	100%
	Squamous NSCLC	0	0%
Type of specimen	Tumour tissue biopsy	20	83%
	Plasma specimen (liquid biopsy)	4	17%
	Both tumour tissue and plasma specimen	0	0%

[c] Figures may not add to 100% due to rounding.

Blueteq data items		N	%
RET fusion partner category	KIF5B	11	46%
	Unknown fusion partner	7	29%
	CCDC6	3	13%
	Another fusion partner	2	8%
	NCOA4	1	4%
	RELCH	0	0%
Previous immunotherapy/platinum-based chemotherapy for NSCLC	The patient has received 1st line combination treatment of platinum-based chemotherapy with immunotherapy for locally advanced or metastatic NSCLC with or without 2nd line cytotoxic chemotherapy	17	71%
	The patient has received 1st line platinum based cytotoxic chemotherapy for locally advanced or metastatic NSCLC with or without 2nd line cytotoxic chemotherapy	4	17%
	The patient has received 1st line platinum based cytotoxic chemotherapy for locally advanced or metastatic NSCLC followed by 2nd line immunotherapy monotherapy with or without further cytotoxic chemotherapy	1	4%
	The only treatment that the patient has received is 1st line immunotherapy monotherapy for locally advanced or metastatic NSCLC	1	4%
	The only treatment that the patient has received is 1st line platinum-based cytotoxic chemotherapy for locally advanced or metastatic NSCLC	1	4%
Brain/CNS metastases	The patient has never had known brain or CNS metastases	20	83%
	The patient has brain secondaries which have not been treated with surgery or radiotherapy and is currently symptomatically stable	2	8%
	The patient has had brain or CNS metastases treated before with surgery or radiotherapy and is currently symptomatically stable	2	8%

Treatment duration

Of the 24 patients with CDF applications, four (16%) were identified as having completed treatment by 31 May 2023 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with selpercatinib in at least three months (see Table 10). The median follow-up time in SACT was 7.4 months (225 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 18.1 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 19.1 months. SACT follow-up ends 31 May 2023.

Table 6: Breakdown by patients' treatment status [d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	2	8%
Treatment stopped	2	8%
Treatment ongoing	20	83%
Total	24	100%

[d] Figures may not sum to 100% due to rounding.
[e] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

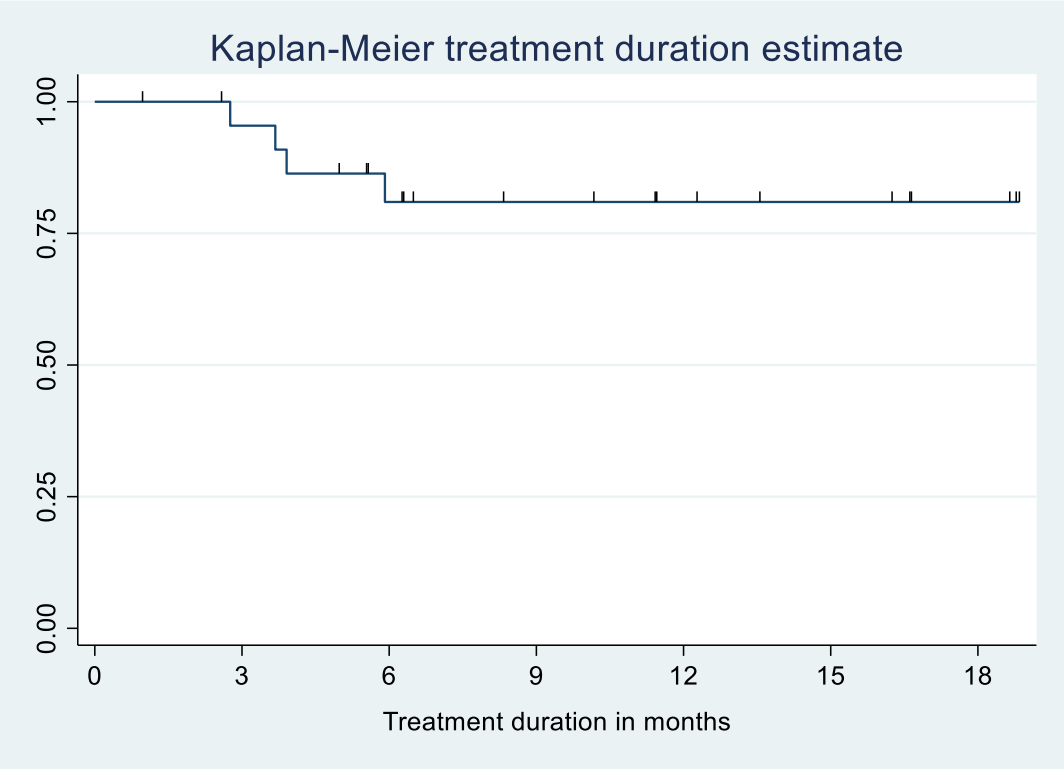
Table 7: Treatment duration at 6-month interval[g]

Time period	Treatment duration (%)
6 months	81% [95% CI: 58%, 93%]

Treatment duration at 12 and 18 months was not included as no events occurred after 6 months.

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration was not reached.

Figure 3: Kaplan-Meier treatment duration (N=24)



[g] Please note low numbers will reduce the chance of statistically significant and robust results.

Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 18.1 months (550 days). SACT contains more follow-up for some patients.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	24	21	15	11	8	6	3

Table 9 shows that for all patients who received treatment, 20 were still on treatment (censored) at the date of follow-up and four had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	20	18	15	11	8	6	3
Events	4	3	0	0	0	0	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 17% (N=4) of patients had ended treatment at 31 May 2023.

Table 10: Treatment outcomes for patients that have ended treatment (N=4)[h,i]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	2	50%
Stopped treatment – acute toxicity	1	25%
Stopped treatment – palliative, patient did benefit	1	25%
Total	4	100%

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=4)

Outcome[j]	Patient died [k] not on treatment	Treatment stopped
Stopped treatment – progression of disease	2	
Stopped treatment – acute toxicity		1
Stopped treatment – palliative, patient did benefit		1
Total	2	2

[h] Figures may not sum to 100% due to rounding.
[i] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[j] Relates to outcomes submitted by the trust in Table 10
[k] Relates to treatment status in Table 6 for those that have ended treatment.

Overall survival (OS)

Of the 24 patients with a treatment record in SACT, the minimum follow-up was 3.9 months (118 days) from the last CDF application. Patients were traced for their vital status on 28 September 2023. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 10.2 months (310 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6, 12-month intervals[l]

Time period	OS (%)
6 months	96% [95% CI: 73%, 99%]
12 months	91% [95% CI: 67%, 98%]

OS at 18 months was not included as no events occurred after 7 months.

[l] Please note low numbers will reduce the chance of statistically significant and robust results.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 28 September 2023. The median OS was not reached.

Figure 4: Kaplan-Meier survival plot (N=24)

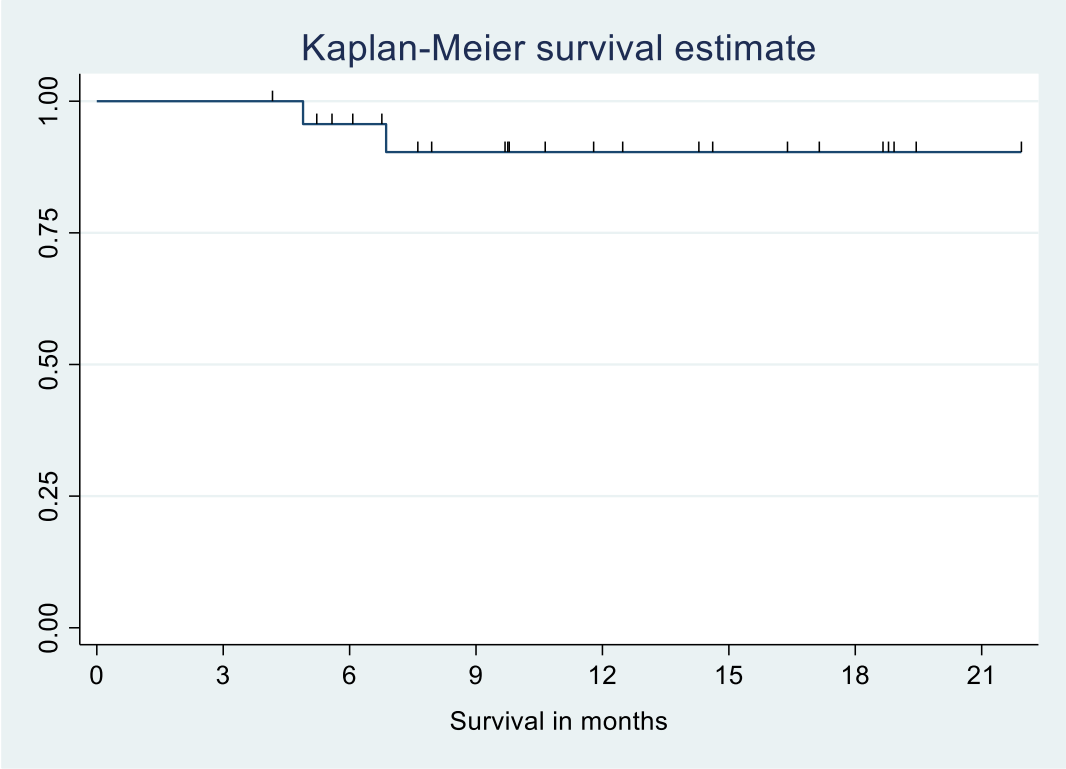


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 22.1 months (672 days), all patients were traced on 28 September 2023.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21	21
Number at risk	24	24	20	15	10	7	5	1

Table 14 shows that for all patients who received treatment, 22 were still alive (censored) at the date of follow-up and two had died (events).

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21	21
Censored	22	22	19	15	10	7	5	1
Events	2	2	1	0	0	0	0	0

5. Conclusions

Twenty-five patients received selpercatinib for the treatment of RET fusion-positive NSCLC [TA760] through the CDF in the reporting period (25 November 2021 to 31 May 2023). Twenty-four patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 96%. An additional patient with a CDF application did not receive treatment, this was confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset show that 38% (N=9) of patients that received selpercatinib for the treatment of RET fusion-positive NSCLC were male, 63% (N=15) of patients were female. 75% of the cohort were aged between 50 and 79 over, (N=18) and 67% (N=16) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 17% (N=4) of patients were identified as no longer being on treatment. Of these four patients:

- 50% (N=2) of patients stopped treatment due to progression of disease
- 25% (N=1) of patients stopped treatment due to acute toxicity
- 25% (N=1) of patients were treated palliatively and did benefit from the treatment they received

Median treatment duration was not reached. 81% of patients were still receiving treatment at 6 months [95% CI: 58%, 93%].

The median OS was not reached. OS at 6 months was 96% [95% CI: 73%, 99%] and OS at 12 months was 91% [95% CI: 67%, 98%].

6. References

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer

(MA review of TA760) [ID6293]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating RET fusion-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Yvonne Summers
2. Name of organisation	The Christie
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with RET fusion-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for RET fusion-positive advanced non-small-cell lung cancer or the technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil

8. What is the main aim of treatment for RET fusion-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To induce response, improve disease related symptoms, maintain QoL, delay progression, improve progression free survival and overall survival
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Partial response is defined by recist as a 30% reduction in target lesion diameters, but more minor responses and prolonged disease stability are clinically significant
10. In your view, is there an unmet need for patients and healthcare professionals in RET fusion-positive advanced non-small-cell lung cancer?	At present patients have access to gold standard clinical care with RET targeted therapy (Selpercatinib) either in first line (preferrable, via CDF) or following platinum based chemotherapy +/- immunotherapy (TA760) Selpercatinib is an excellent option for front line therapy and is currently available via the CDF, if it was not available then chemotherapy based treatments which are less effective more toxic would need to be used.
11. How is RET fusion-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	GUIDELINES: • NICE (TA 760) • ESMO (https://doi.org/10.1016/j.annonc.2022.12.009) and NCCN guidelines version 7.2024 recommends first line targeted therapy as the preferred option with Selpercatinib or Pralsetinib, or as second line therapy if other chemotherapy or immunotherapy has been used initially. • ASCO guideslines updated Oct 2022 (https://ascopubs.org/doi/full/10.1200/JCO.22.00824#fig1) support 1st and 2nd line therapy with Selpercatinib and Pralsetinib, but classify the evidence base for the two drugs as moderate and weak respectively The clinical pathways are well defined however the main challenge is ensuring that all patients have full molecular test results available before initiation of first line therapy, either because of time taken to have all test results available or because of insufficient biopsy material for full testing.

	The NHS England ctDNA testing in NSCLC programme will help identify more patients in a timely fashion. There is still a small but important cohort of patients who do not access Selpercatinib first line due to failures of testing and time taken to receive results
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is currently used as SoC in the NHS in first and second line setting via the CDF and TA760. No Secondary care NA – technology is in use
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	N/A If this option were not available it would be of substantial detriment to a small number of patients where NHS systems had failed to provide a result of molecular testing for RET prior to initiation of treatment.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/A as this is a review of TA 760
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	This is a current SoC for patients who have not accessed first line selpercatinib. Having access to treatment after non-targeted therapy remains important as a

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	number of patients do not have their RET status available prior to initiation of frontline therapy. As a current SoC there are no practical considerations of this review
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No – treatment continues until clinically relevant progression, intolerable side effects or patient choice
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	N/A as this is a review of TA 760
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	N/A as this is a review of TA 760
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?	N/A as this is a review of TA 760

Clinical expert statement

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	BLUTEQ forms will inform this question more reliably than individual clinical experts. My personal view (of a handful of patients) is that UK patients have similar outcomes to the trial data
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Data from NHSE as above
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA347]?	No
23. How do data on real-world experience compare with the trial data?	https://doi.org/10.1016/j.jtho.2023.02.00 Aldea et al. reported on outcomes of 218 patients with RET+ NSCLC treated at 31 cancer centres. In this primarily European cohort of patients RET tyrosine kinase inhibitors (TKIs), administered in most patients (~75%) and use of RET TKIs was associated with higher response rate (76%) significantly improved overall survival.
24. Are the following baseline characteristics prognostic factors and/or treatment effect modifiers? How would differences in these characteristics affect outcomes and how well people respond to treatments for previously-treated advanced NSCLC? • ***RET fusion status***	None of these can reliably be used to predict outcomes and response. Patients respond in both first line and beyond. Time since diagnosis is often a marker of the "biological aggressiveness" of cancer but this cannot be used to guide management.

• ***Line of treatment*** • ***Female*** • ***Never smoked*** • ***Asian ethnicity*** • ***Time since diagnosis***	
25. How long would people be expected to stay on treatment with the technology if they remained progression free?	NHSE and BLUTEQ forms will provide UK real world data Trial data has been updated in J Clin Oncol 2023 Jan 10;41(2):385-394. doi: 10.1200/JCO.22.00393. At median follow up of 24.7 months 247 patients who had had previous platinum doublet chemotherapy had a response rate of 61% a median PFS of 24.9 months (19.3-NE), and the median duration of response was 28.6 months.
26. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	No

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Up to 30% of patients may not have full molecular testing results available at the time of initiation of treatment

For some patients there is insufficient biopsy material available to complete a full panel of tests and the patient may not be well enough to undergo a second or third biopsy

These patients may be started on a non-targeted, chemotherapy based treatment rather than the target treatment

It is important that Selpercatinib remains the next line of therapy in the unfortunate cases when this occurs

Thank you for your time.

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.

EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (MA review of TA760) [ID6293]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR166385

Completed 20 June 2024
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CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Selpercatinib for previously treated RET fusion-positive advanced non-small cell lung cancer (MA review of TA760) [ID6293]

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Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical and statistical evidence and supervised the final report
Angela Stainthorpe	Critical appraisal of the economic model
Sophie Beale	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Marty Chaplin	Critical appraisal of the statistical evidence
Rebecca Bresnahan	Critical appraisal of the clinical evidence
James Mahon	Critical appraisal of the economic model
Yenal Dundar	Critical appraisal of the 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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AE	adverse event
ALK	anaplastic lymphoma kinase
CI	confidence interval
CS	company submission
BID	twice daily
CDF	Cancer Drugs Fund
CNS	central nervous system
DoR	duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire C-30
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
HRQoL	health-related quality of life
IAS	Integrated Analysis Set
ICER	incremental cost-effectiveness ratio
IRC	independent review committee
MAIC	matching adjusted indirect comparison
MKI	multi-kinase inhibitor
n/a	not applicable
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
OS	overall survival
OSAS	Overall Safety Analysis Set
PD	progressed disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PF	progression-free
PFS	progression-free survival
PSS	Personal Social Services
QALY	quality-adjusted life year
RCT	randomised controlled trial
RET	rearranged during transfection
ROS-1	c-ros oncogene 1
SACT	systemic anti-cancer therapy
SLR	systematic literature review
TA	technology appraisal
TPS	tumour proportion score
TSD	Technical Support Document
TTD	time to treatment discontinuation

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Limitations of the evidence base: population and comparators	2.6.1 and 2.6.3
Issue 2	Company (pseudo-control) docetaxel arm does not provide robust comparator data	3.7.1
Issue 3	Limitations of the company network meta-analyses	3.7.2
Issue 4	Limitations of unanchored MAICs	3.7.3
Issue 5	Company cost effectiveness results were generated by comparator data that are not robust	3.7 and 6.1.1
Issue 6	Company may have over-estimated the cost of treatment with selpercatinib	6.4
Issue 7	Size of severity modifier	6.5

EAG=External Assessment Group; MAICs=matching-adjusted indirect comparison

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

The company has presented cost effectiveness results for the comparison of selpercatinib versus (pseudo-control) docetaxel and versus nintedanib+docetaxel. The EAG made two revisions to the company model:

- generated progression-free survival (PFS) estimates using the spline knot 1 distribution
- adjusted the selpercatinib starting dose so that it reflects the baseline LIBRETTO-001 trial dose

The EAG also explored the impact on cost effectiveness results of running a selpercatinib treatment discontinuation scenario.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Limitations of the evidence base: population and comparators

Report section	2.6.1 and 2.6.3
Description of issue and why the EAG has identified it as important	All the selpercatinib effectiveness and safety data are derived from a phase I/II single-arm trial of patients with RET fusion-positive NSCLC. There is no comparator effectiveness and safety data for patients with RET fusion-positive NSCLC.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on whether RET fusion status is an important prognostic factor and/or treatment effect modifier.

EAG=External Assessment Group; NSCLC=non-small cell lung cancer; RET=rearranged during transection

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Company (pseudo-control) docetaxel arm does not provide robust comparator data

Report section	3.7.1
Description of issue and why the EAG has identified it as important	The company created a (pseudo-control) docetaxel arm (REVEL trial data; one prior treatment: 100%; median OS follow up=8.8 months) to allow selpercatinib (LIBRETTO-001 trial data; ≥2 prior treatments: [redacted]%; median OS follow up: [redacted] months) to be connected to the NMA networks of evidence. This arm was created using PSM. The company was not able to match for RET fusion-positive status or line of treatment because all LIBRETTO-001 trial patients had RET fusion-positive NSCLC and all REVEL trial patients had only received one previous line of treatment. Further, even after matching variables that could be matched, potentially important baseline patient characteristic imbalances remained, and these could bias selpercatinib versus (pseudo-control) docetaxel treatment effect estimates (ORR, PFS and OS).
What alternative approach has the EAG suggested?	The PSM approach may be improved by using statistical methods to improve overlap and adjust for differences in patient characteristics. However, the EAG considers that, as it was not possible to match for RET fusion-status or line of treatment, utilising such techniques may not generate robust treatment effect estimates. The EAG asked the company to carry out unanchored MAICs; these do not require (pseudo-control) docetaxel data. See Issue 4 for details.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on whether RET fusion status, line of treatment and other patient characteristic imbalances are important prognostic factors and/or treatment effect modifiers.

EAG=External Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PSM=propensity score matching; RET=rearranged during transection

Issue 3 Limitations of the company network meta-analyses

Report section	3.7.2
Description of issue and why the EAG has identified it as important	The company provided ORR, PFS and OS NMA results for selpercatinib versus docetaxel and versus nintedanib+docetaxel. The robustness of these results is uncertain as: • all comparator studies included patients with unknown RET fusion-positive NSCLC • (pseudo-control) docetaxel was included in the networks • baseline characteristics were not presented for the studies included in the NMAs • length of follow-up and number of prior treatments varied • the networks included many studies of irrelevant comparators (potentially increasing heterogeneity) • data from patients in one study are included in the NMAs twice • the proportional hazards assumption may not hold for some studies (PFS: n=3; OS: n=2) • it was not possible to conduct thorough explorations of heterogeneity • the impact of inconsistency is uncertain
What alternative approach has the EAG suggested?	The EAG asked the company to carry out unanchored MAICs to explore the robustness of the company's indirect clinical effectiveness results. See Issue 4 for details.
What is the expected effect on the cost effectiveness estimates?	See Issue 4 for details.
What additional evidence or analyses might help to resolve this key issue?	None. The EAG considers that, without robust comparator evidence (see Issue 2) it is not possible to generate robust NMA results.

EAG=External Assessment Group; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RET=rearranged during transection

Issue 4 Limitations of unanchored MAICs

Report section	3.7.3
Description of issue and why the EAG has identified it as important	In response to clarification question A1, the company provided ORR, PFS and OS unanchored MAIC results for selpercatinib versus docetaxel and versus nintedanib+docetaxel. The robustness of these results is uncertain as: • the comparator study (LUME-Lung 1 trial) included patients with unknown RET fusion-positive NSCLC treated in the second-line only setting • it is unclear whether some potentially important baseline patient characteristics were well balanced across the treatment arms after matching and adjusting (e.g., ethnicity, median time from diagnosis and other potentially important prognostic factors and/or effect modifiers which may not have been measured); imbalances in these characteristics could result in residual bias • it is unclear whether the proportional hazards assumption holds for OS • ORR unadjusted MAIC results are very different from propensity score matching and NMA ORR results
What alternative approach has the EAG suggested?	The EAG asked the company to carry out unanchored MAICs to explore the robustness of the company's indirect clinical effectiveness results. However, due to insufficient information about the methods, it has not been possible to provide full critique of the company approach.
What is the expected effect on the cost effectiveness estimates?	The company has not generated cost effectiveness results using unanchored MAIC results. For the comparison of selpercatinib versus comparators, unanchored PFS and OS MAIC results are more favourable than NMA results. Therefore, using unanchored MAIC results in the company model would generate more favourable selpercatinib cost effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	Further consideration of the potential impact of residual bias would be informative. However, the EAG highlights that it would still not be possible to match and adjust for RET fusion status or line of treatment.

EAG=External Assessment Group; MAIC=matching-adjusted indirect comparison; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RET=rearranged during transection

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 5 Company cost effectiveness results, selpercatinib versus (pseudo-control) docetaxel, may not be robust

Report section	3.7.1 and 6.1.1
Description of issue and why the EAG has identified it as important	The (pseudo-control) docetaxel comparator clinical effectiveness evidence presented by the company may not be robust (see Issue 2). The EAG considers that without robust docetaxel data, it is not possible to generate robust cost effectiveness results for selpercatinib versus comparators.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on whether RET fusion status, line of treatment and other patient characteristic imbalances are important prognostic factors and/or treatment effect modifiers.

EAG=External Assessment Group; RET=rearranged during transfection

Issue 6 Company may have over-estimated the cost of treatment with selpercatinib

Report section	6.4
Description of issue and why the EAG has identified it as important	The company has generated TTD estimates for patients treated with selpercatinib based on LIBRETTO-001 trial TTD data. This approach results in some patients being treated in the PD health state for substantially more than 3 months, and some patients in the PFS state being treated for 20 years.
What alternative approach has the EAG suggested?	Based on clinical advice to the EAG that patients who remain progression-free will not be treated with selpercatinib for 20 years, the EAG ran a scenario in which treatment was stopped at 10 years. This EAG scenario does not address the issue of any difference between LIBRETTO-001 trial and NHS level of treatment after disease progression.
What is the expected effect on the cost effectiveness estimates?	This change reduces the cost of treatment with selpercatinib and reduces the ICERs per QALY gained for the comparison of selpercatinib versus comparators; however, the validity of these results is uncertain as the effect on patients of stopping treatment early is unknown.
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PD=progressed disease; QALY=quality adjusted life year; TTD=time to treatment discontinuation

1.6 Other key issues: summary of the EAG's view

Issue 7 Size of severity modifier

Report section	6.5
Description of issue and why the EAG has identified it as important	The EAG and the company agree that a severity modifier of 1.2 is appropriate. However, the company has also presented a case for considering the use of a 1.7 multiplier.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	The higher the multiplier, the lower the ICERs per QALY gained for the comparison of selpercatinib versus comparators
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

1.7 Summary of EAG's preferred assumptions and resulting ICERs

Table B Probabilistic pairwise results (selpercatinib versus (pseudo-control) docetaxel), PAS price for selpercatinib

EAG revisions	Incremental		ICER		
	Cost	QALYs	£/QALY	£/QALY*1.2	£/QALY*1.7
A1. Company base case (clarification model)	[redacted]	[redacted]	£63,723	£53,102	£37,484
A2. EAG corrected base case	[redacted]	[redacted]	£64,370	£53,642	£37,865
B. EAG preferred base case	[redacted]	[redacted]	£64,403	£53,669	£37,884

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table C Probabilistic pairwise results (selpercatinib versus nintedanib+docetaxel), PAS price for selpercatinib

EAG revisions	Incremental		ICER		
	Cost	QALYs	£/QALY	£/QALY*1.2	£/QALY*1.7
A1. Company base case (clarification model)	[redacted]	[redacted]	£57,081	£47,567	£33,577
A2. EAG corrected base case	[redacted]	[redacted]	£65,123	£54,269	£38,308
B. EAG preferred base case	[redacted]	[redacted]	£65,076	£54,230	£38,280

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table D Company clarification base case probabilistic results (fully incremental analysis), PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained (1.2 severity modifier)
(Pseudo-control) docetaxel	[redacted]	[redacted]	
Nintedanib+docetaxel	[redacted]	[redacted]	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£53,102

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table E EAG preferred base case probabilistic results (fully incremental analysis), PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained (1.2 severity modifier)
(Pseudo-control) docetaxel	[redacted]	[redacted]	
Nintedanib+docetaxel	[redacted]	[redacted]	£46,861
Selpercatinib	[redacted]	[redacted]	£54,230

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Modelling errors identified and corrected by the EAG are described in Section 6.1.2. For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In 2021, a National Institute for Health and Care Excellence (NICE) Appraisal Committee (AC) reviewed the clinical and cost effectiveness of selpercatinib (brand name: Retsevmo) as a treatment option for adults with advanced (Stage IIIB to Stage IV) rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy after disease progression (TA760[1]). At the time of the original appraisal, the NICE AC was unable to recommend the routine use of selpercatinib in NHS clinical practice. Therefore, in January 2022, NICE recommended selpercatinib (TA760[1]) within the Cancer Drugs Fund (CDF) as a treatment option for adults with advanced RET fusion-positive NSCLC who require systemic therapy after immunotherapy, platinum-based chemotherapy or both, if the conditions in the Managed Access Agreement[2] (MAA) for selpercatinib were followed. This appraisal is part of the CDF exit process. It focuses on updated (longer term) selpercatinib clinical effectiveness data (LIBRETTO-001 trial[3]) and cost effectiveness results presented by the company.

In this External Assessment Group (EAG) report, reference to the company submission (CS) is to the company's Document B, which is the company's full evidence submission for this CDF review. Additional evidence was provided by the company during the clarification stage.

2.2 Non-small cell lung cancer (NSCLC)

Lung cancer is the second most common cancer in England; 34,478 people were diagnosed in England in 2021.[4,5] Lung cancer is the most common cause of cancer-related death in England;[6] in 2017, the age standardised mortality rate for men and women was 58 per 100,000 and 43 per 100,000, respectively.[7]

Lung cancer is made up of NSCLC, which accounts for around 80% to 85% of all lung cancer cases in England,[8] and small cell lung cancer.[9] NSCLC is split into two main histological types: non-squamous type carcinomas and squamous type carcinomas.[10] Non-squamous type carcinomas represent around 70% of all NSCLC cases[9] and can be divided into two main histological subtypes: adenocarcinoma (40% of all lung cancer cases) and large cell carcinoma (10% to 15% of all lung cancer cases).[10]

2.3 RET fusion-positive *NSCLC*

NSCLC can be further classified by 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

and RET fusions.[11] Patients with oncogene-driven NSCLC typically have just one genetic marker, as these mutations are typically mutually exclusive.[12] Patients with RET fusion-positive NSCLC represent 1% to 2% of all NSCLC cases.[13] RET fusion mutations most commonly occur in adenocarcinomas but have also been identified in tumours of mixed histology[13] and, rarely, in squamous carcinomas.[14,15]

RET is a transmembrane receptor tyrosine kinase that is expressed by multiple tissue types, including lung, adrenal medulla and thyroid.[13] In healthy people, RET protein is involved in cell growth, cell division and cell differentiation.[16] Abnormal activity of RET protein in cancer is caused by mutations and fusions to the gene (RET) encoding the RET protein. In NSCLC, gene fusions are the most common type of mutation to occur to the RET gene. RET fusions increase the activity of the RET kinase domain which leads to increased activation of downstream signalling pathways involved in cell survival, proliferation, migration and angiogenesis. [13,17]

Patients with RET fusion-positive NSCLC are usually aged ≤60 years and include former smokers, as well as those who have never smoke.[18] The EAG is not aware of any studies that have investigated the prevalence or demographic characteristics of patients with RET fusion-positive NSCLC in the UK. Evidence from a meta-analysis (Lin 2015[19]) of nine epidemiological studies (including 6899 patients with NSCLC and 84 patients with RET fusion-positive NSCLC) suggests that RET fusions are more common in women than men, in younger people than in older people and in non-smokers than smokers, and that these differences were most strongly observed in people of Asian ethnicity.

The prognosis for patients with NSCLC depends on disease stage at diagnosis. Nearly half (46.8%) of patients with NSCLC are diagnosed with Stage IV disease[20] and the 1-year survival rate for these patients is 45%.[5] As highlighted in the CS (pp20-21), it is unclear if RET fusion status is a prognostic factor. Analysis of the US Flatiron-Foundation Medicine Clinico-Genomics database by Hess 2021[21] found no difference in tumour response or progression-free survival (PFS) between patients with RET fusion-positive NSCLC (n=46) versus those with RET fusion-negative NSCLC (n=5761). While overall survival (OS) was improved in patients with RET fusion-positive NSCLC versus those with RET fusion-negative NSCLC, analyses adjusted for baseline covariates found no difference in OS.

2.4 Company's overview of current service provision

Clinician feedback during TA760[22] and clinical advice to the company for this appraisal was that immunotherapy and/or platinum-based chemotherapies are commonly used as first-line treatments for patients with RET fusion-positive NSCLC (CS, p24). Patients may then receive

immunotherapy (if this was not received first-line) or chemotherapy, including platinum-based chemotherapy or docetaxel-based chemotherapy (docetaxel monotherapy or nintedanib+docetaxel). Clinical advice to the EAG agrees with this clinical feedback and advice.

Current treatment options routinely available in NHS clinical practice are summarised in Table 1. It is important to note:

- clinical advice to the EAG is that immunotherapy (alone or in combination with platinum-based chemotherapy) is the most common first-line treatment option (for approximately 75% of patients); the limited data from the Systemic Anti-Cancer Therapy (SACT) dataset[23] collected as part of the selpercatinib MAA[2] also showed immunotherapies with/without platinum-based chemotherapies are the most commonly used ([redacted]) first-line treatments for patients with RET fusion-positive NSCLC (see Section 2.5.5)
- an immunotherapy (pembrolizumab, atezolizumab or nivolumab) would not be an option as a second-line or later treatment if it had been used earlier in the treatment pathway
- none of the treatments in Table 1 are specifically targeted treatments for patients with advanced RET fusion-positive NSCLC; selpercatinib is the only currently available RET targeted treatment but, as it is only recommended with managed access (TA911)[24] or via the CDF (TA760),[1] it is not considered as routine NHS clinical practice (further information about selpercatinib is provided in Section 2.5)

Given the rarity of RET fusion-positive NSCLC with a squamous histology, the company has focussed on patients with a non-squamous histology in this appraisal. Furthermore, the company highlights (CS, p26) that RET-rearranged lung cancers are characterised by low levels of programmed death-ligand 1 (PD-L1) expression; therefore the most relevant treatment pathways shown in Table 1 are for patients with non-squamous NSCLC and PD-L1<50%.

Table 1 Treatment options in routine NHS clinical practice for patients with advanced RET fusion-positive NSCLC (NG122)

First-line	Second-line	Third-line
Non-squamous, PD-L1<50%		
Platinum doublet chemotherapy followed by pemetrexed maintenance (TA190)[25] or Pemetrexed+cisplatin (TA181)[26] followed by pemetrexed maintenance (TA402)[27] or Pemetrexed+carboplatin followed by pemetrexed maintenance	Pembrolizumab (TA428)[28] or Atezolizumab (TA520)[29] or Nivolumab (TA655)[30] or Nintedanib+docetaxel (TA347)[31] or Docetaxel	Nintedanib+docetaxel (TA347)[31] or Docetaxel

First-line	Second-line	Third-line
Pembrolizumab+pemetrexed +platinum chemotherapy or Atezolizumab+bevacizumab +carboplatin+paclitaxel	Nintedanib+docetaxel (TA347)[31] or Docetaxel	None
Non-squamous, PD-L1≥50%		
Pembrolizumab+pemetrexed +platinum chemotherapy (TA683)[32]	Nintedanib+docetaxel (TA347)[31] or Docetaxel	None
Pembrolizumab (TA531)[33] or Atezolizumab (TA705)[34]	Platinum doublet chemotherapy followed by pemetrexed maintenance (TA190)[25] or Pemetrexed+cisplatin (TA181)[26] followed by pemetrexed maintenance (TA402)[27] or Pemetrexed+carboplatin followed by pemetrexed maintenance	Nintedanib+docetaxel (TA347)[31] or Docetaxel
Squamous, PD-L1<50%		
Platinum doublet chemotherapy	Pembrolizumab (TA428)[28] or Atezolizumab (TA520)[29] or Nivolumab (TA655)[30] or Docetaxel	Pembrolizumab (TA428)[28] or Atezolizumab (TA520)[29] or Nivolumab (TA655)[30] or Docetaxel
Pembrolizumab+carboplatin +paclitaxel (TA770)[35]	Docetaxel	None
Squamous, PD-L1≥50%		
Pembrolizumab+carboplatin +paclitaxel (TA770)[35] **Only if urgent clinical intervention needed**	Docetaxel	None
Pembrolizumab (TA531)[33] or Atezolizumab (TA705)[34]	Platinum doublet chemotherapy	Docetaxel

Note: Where the treatment option has been appraised by NICE as a Single Technology Appraisal, the TA number is denoted
NHS=National Health Service; NSCLC=non-small cell lung cancer; NG=national guideline; NICE=National Institute for Health and Care Excellence; PD-L1=programmed death-ligand 1; RET=rearranged during transfection; TA=technology appraisal
Source: NG122, interactive PDF, March 2024[36]

2.5 Selpercatinib

2.5.1 Selpercatinib mechanism of action

Selpercatinib is a selective kinase inhibitor; 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.

2.5.2 Selpercatinib licensing and dosing

Selpercatinib as monotherapy currently has the following therapeutic indications approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of:[37,38]

- adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor
- adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib
- adults and adolescents aged ≥12 years with RET-mutant medullary thyroid cancer.

Relevant to the current appraisal, a conditional marketing authorisation was initially granted by the MHRA in February 2021 for use as monotherapy for the treatment of patients with advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. This wording was replaced by the current wording in October 2022 and the 'previously treated with immunotherapy and/or platinum-based chemotherapy' indication (as per TA760[1]) incorporated within the current indication.

Selpercatinib is administered orally and is available as 40mg and 80mg hard capsules. The recommended dose is 120mg twice daily (BID) for patients who weigh <50kg and 160mg BID for patients who weigh ≥50kg; dose interruptions or reductions are recommended for patients experiencing some adverse effects.

2.5.3 NICE recommendations for selpercatinib for RET fusion-positive NSCLC

In January 2022, NICE recommended selpercatinib for use within the CDF as a treatment option for adults with advanced RET fusion-positive NSCLC who require systemic therapy after immunotherapy, platinum-based chemotherapy or both (TA760[1]).

In July 2023, NICE recommended selpercatinib as a treatment option for adults with untreated RET fusion-positive NSCLC, if the conditions set out in the MAA for selpercatinib are followed (TA911).[24]

Should selpercatinib be recommended by NICE as first-line treatment option for routine NHS clinical practice, the company considers it would normally be used first-line, rather than later along the treatment pathway. It would mainly only be used later along the treatment pathway for patients with RET fusion-positive NSCLC whose RET status was unknown when first-line treatment was required. Clinical advice to the EAG agrees with the company.

2.5.4 Uncertainties with selpercatinib data identified in TA760

The NICE TA760[1] AC concluded that, based on the limited clinical effectiveness data available, significant uncertainty regarding the clinical effectiveness of selpercatinib remained. The NICE AC was unable to recommend routine use of selpercatinib in NHS clinical practice due to the "key uncertainties" regarding the accuracy and clinical feasibility of the extrapolations of PFS, time to treatment discontinuation (TTD) and OS for selpercatinib and PFS and OS for docetaxel, which were based on a simulated pseudo-control arm.

The NICE AC was however satisfied that, with the commercial access agreement proposed by the company applied to selpercatinib, selpercatinib had plausible potential to be cost effective. Therefore, the NICE AC concluded that selpercatinib met the criteria for inclusion in the CDF and recommended its use within the CDF for treating RET fusion-positive advanced NSCLC in adults who need systemic therapy after immunotherapy and/or platinum-based chemotherapy, if the conditions in the MAA[2] were followed. The MAA[2] conditions included an obligation to collect real-world data (see Section 2.5.5).

The NICE AC considered that further LIBRETTO-001 trial[3] data collection may reduce the uncertainties in the PFS, TTD and OS extrapolations for selpercatinib but not in the PFS and OS extrapolations for docetaxel. The NICE AC agreed that all uncertainties would not be fully resolved by data collection in the CDF.

The NICE AC stated that when the TA760[1] guidance is reviewed, the company should use the committee's preferred assumptions, unless new evidence indicates otherwise. The AC's preferred assumptions included modelling the cost of selpercatinib based on TTD rather than on PFS since TTD was a key driver of cost effectiveness.

2.5.5 Summary of selpercatinib real-world data collected (SACT dataset)

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). NHS England evaluated the real-world treatment effectiveness of selpercatinib in the CDF population, during the managed access period, and these data are available in the form of a SACT dataset. The SACT report[23] was provided by the company as part of the CS reference pack. Between [redacted] and [redacted], there were [redacted]

applications to receive selpercatinib via the CDF; data from [redacted] unique patients were included in the SACT dataset and analyses were conducted for [redacted] patients.

The results from the analysis of baseline characteristics showed:

- [redacted] patients had non-squamous NSCLC
- most [redacted] patients never had known brain or central nervous system (CNS) metastases
- most [redacted] patients were women
- most [redacted] patients were aged 50 years and over
- Eastern Cooperative Oncology Group (ECOG) performance status was [redacted] patients
- most [redacted] patients had received prior treatment with platinum-based chemotherapy plus immunotherapy as a first-line treatment, [redacted] received immunotherapy alone; only [redacted] had not received any prior immunotherapy at all, either first-line or second-line

At data cut-off, [redacted] patients were identified as no longer being on treatment. Reasons for stopping treatment were:

- [redacted]
- [redacted]
- [redacted]

Median OS was [redacted]. At 6 months, the OS rate was [redacted], 95% confidence interval (CI): [redacted] and at 12 months the OS rate was [redacted], 95% CI: [redacted].

Given selpercatinib has only been available via the CDF for patients who need systemic therapy after immunotherapy and/or platinum-based chemotherapy since 2022 and given only [redacted] ([redacted]) patients were identified as no longer being on treatment, the EAG agrees with the company (CS, p50) that SACT data are currently not sufficiently mature to inform this submission.

2.6 Critique of company's definition of decision problem

The key elements of the final scope issued by NICE, and the decision problem addressed by the company, are presented in Table 3. More information regarding the key issues relating to the decision problem is provided in Sections 2.6.1 to 2.6.6.

The primary source of the selpercatinib clinical effectiveness evidence presented by the company was the LIBRETTO-001 trial.[3] The LIBRETTO-001 trial[3] is an ongoing, multicentre, open-label, phase I/II basket trial that enrolled patients with solid tumours treated with selpercatinib, including patients with NSCLC. Patients enrolled in the LIBRETTO-001 trial[3] who had RET fusion-positive NSCLC and progressed on or were intolerant to ≥1 prior standard

first-line therapy are relevant to this appraisal; this included patients in the Integrated Analysis Set (IAS), all of whom had received prior treatment with platinum-based chemotherapy ([redacted] and/or immunotherapy ([redacted]. Phase I of the LIBRETTO-001 trial[3] was a dose escalation phase, while phase II was a dose expansion phase (see Section 3.2.2). The key trial characteristics are presented in Table 2.

Table 2 Key characteristics of the LIBRETTO-001 trial*

Study design	Start date	Intervention	Population(s) for which evidence is presented in this appraisal
On-going, multi-centre, open-label, phase I/II single arm basket trial	May 2017	Selpercatinib (n=[redacted])	• Integrated Analysis Set: patients with previously treated, advanced RET fusion-positive NSCLC (n=[redacted]) • Overall Safety Analysis Set: all patients regardless of tumour type or treatment history (n=[redacted])*

* The overall LIBRETTO-001 trial[3] population includes patients with RET fusion-positive NSCLC, pancreatic cancer and colorectal cancer as well as patients with other agnostic tumours with RET activation
n/a=not applicable; NSCLC=non-small cell lung cancer; RET=rearranged during transfection

The LIBRETTO-001 trial[3] provides the pivotal trial data included in the company's European Medicines Agency (EMA) application[39] and Summary of Product Characteristics (SmPC);[37,38] data from this trial were also used to inform TA760.[1] The EMA[39] has requested phase III evidence for patients with RET fusion-positive NSCLC; this is being collected in the phase III LIBRETTO-431 trial[40] (treatment-naïve patients with RET fusion-positive NSCLC).

The LIBRETTO-001 trial[3] data that informed the EMA application,[39] SmPC[37,38] and TA760[1] were sourced from the 16 December 2019 data-cut-off; 531 patients had been enrolled into the trial (Overall Safety Analysis Set [OSAS]) and 184/531 of these patients were enrolled into the IAS, i.e., patients who had received prior treatment with platinum-based chemotherapy and/or immunotherapy). Evidence from the 13 January 2023 data-cut has been used to inform this appraisal. The sizes of the OSAS and IAS in this dataset had increased to n=[redacted] and n=[redacted], respectively. For IAS patients, median PFS follow-up increased from [redacted] months to [redacted] months and median OS follow-up had increased from [redacted] months to [redacted] months (CS, Table 5).

Table 3 Key elements of the decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS with company rationale where different to scope	EAG comment
Population	Adults with RET fusion-positive advanced NSCLC that has been previously treated but has not been treated with a RET inhibitor.	Adults with previously treated advanced, non-squamous, RET fusion-positive NSCLC who require systemic therapy but who have not been previously treated with a RET inhibitor. RET fusions rarely occur in NSCLC tumours with squamous histology, which was acknowledged by the Committee in a previous NICE appraisal of selpercatinib in NSCLC.[1,13] This is reflected by the clinical evidence base underpinning this submission: patients with NSCLC in the pivotal LIBRETTO-001 study were identified to have non-squamous histology in the overwhelming majority of cases. Furthermore, of the [redacted] patients recorded in the SACT dataset to have received selpercatinib, all of them had non-squamous tumour histology.[23] Consequently, the target population in this submission has been restricted to patients with tumours exhibiting non-squamous histology.	The EAG notes that in TA760,[1] the CDF clinical lead stated and the NICE Appraisal Committee concluded that recommendations for the use of selpercatinib should apply to people with squamous and non-squamous advanced NSCLC equally. It was concluded in TA760[1] that the LIBRETTO-001 trial[3] population results were generalisable to NHS patients with RET fusion-positive advanced NSCLC.
Intervention	Selpercatinib	In line with the final NICE scope: Selpercatinib (160mg BID)	As per scope.
Comparator(s)	For people with non-squamous cancer previously treated with platinum doublet chemotherapy or pemetrexed+carboplatin or cisplatin: • atezolizumab • docetaxel • nintedanib+docetaxel For people with PD-L1 positive non-squamous cancer previously treated with platinum doublet chemotherapy or pemetrexed+carboplatin or cisplatin:	For people with non-squamous NSCLC: • docetaxel monotherapy • nintedanib+docetaxel (TA347)[31] This submission will focus on clinical evidence from patients with RET fusion-positive non-squamous NSCLC due to the rarity of RET fusion alterations in squamous disease, and in alignment with the population enrolled in the LIBRETTO-001 clinical trial. Therefore, comparators for the patient population with tumours exhibiting squamous histology are not considered to be relevant to the present scope, as per the approach taken in previous NICE appraisals of selpercatinib in NSCLC (TA760[1]	The EAG agrees with the company that the most relevant comparators for this appraisal are the same as in TA760,[1] namely: • docetaxel • nintedanib+docetaxel The EAG considers that results from the company indirect treatment comparisons of selpercatinib versus (pseudo-control) docetaxel (PSM results, NMA results and unanchored MAIC results) may not be robust.

Parameter	Final scope issued by NICE	Decision problem addressed in the CS with company rationale where different to scope	EAG comment
	• nivolumab • pembrolizumab For people with non-squamous cancer previously treated with pembrolizumab with pemetrexed+platinum chemotherapy or atezolizumab with bevacizumab, carboplatin+paclitaxel: • docetaxel • nintedanib+docetaxel For people with non-squamous cancer previously treated with pembrolizumab or atezolizumab monotherapy: • docetaxel • nintedanib+docetaxel • pemetrexed+carboplatin • pemetrexed+cisplatin • platinum doublet chemotherapy For people with squamous cancer previously treated with platinum doublet chemotherapy: • atezolizumab • docetaxel • nivolumab For people with PD-L1 positive squamous cancer previously treated with platinum doublet chemotherapy: • pembrolizumab	and TA911[24]) and recent feedback from a UK clinical expert.[1,24,41] In further alignment with Committee preferences in the prior NICE appraisal of selpercatinib for previously treated RET fusion-positive advanced NSCLC (TA760[1]), immunotherapies (atezolizumab, nivolumab and pembrolizumab) are not considered to be relevant comparators in the second-line setting in patients with RET fusion-positive non-squamous NSCLC, as patients would be expected to receive immunotherapies as a first-line treatment and so would not receive them again at second line.[1] The same Committee also concluded that pemetrexed+carboplatin and platinum doublet chemotherapy are not relevant comparators in patients with RET fusion-positive non-squamous NSCLC at second-line, as they are rarely used at this point in the treatment pathway.[1] The Committee's conclusion that immunotherapies, pemetrexed+carboplatin and platinum doublet chemotherapy are not relevant comparators to selpercatinib in this indication was supported by clinician feedback during the prior appraisal, and subsequently by more recent clinical expert feedback received during the preparation of this submission.[1,41] As such, in alignment with the Committee conclusions and clinical expert advice, Lilly maintain that docetaxel monotherapy and nintedanib+docetaxel are the only relevant comparators in this indication.[1]	Further, for the comparison of selpercatinib versus nintedanib+docetaxel, company NMA and unanchored MAIC results may not be robust.

Parameter	Final scope issued by NICE	Decision problem addressed in the CS with company rationale where different to scope	EAG comment
	For people with squamous cancer previously treated with pembrolizumab with carboplatin+paclitaxel: • docetaxel For people with squamous cancer previously treated with pembrolizumab or atezolizumab monotherapy: • platinum doublet chemotherapy		
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • TTD • AEs • HRQoL	In line with the NICE final scope Primary: • Objective response rate (ORR) Secondary: • Duration of response (DoR) • PFS • OS • TTD HRQoL: • European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30) Safety outcomes: • AEs	Selpercatinib results for all the listed outcomes are available from the single-arm LIBRETTO-001 trial.[3] Data to allow comparison of the effectiveness of selpercatinib versus other treatments were generated by NMAs for the following outcomes: ORR, PFS and OS. The company's networks have been constructed by connecting LIBRETTO-001 trial[3] data to comparator data via a (pseudo-control) docetaxel arm. In response to clarification question A1 to perform ORR, PFS and OS unanchored MAICs using data from the LIBRETTO-001 trial[3] (selpercatinib) and LUME-Lung 1 trial[42] (docetaxel, nintedanib+docetaxel).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY.	In line with the NICE final scope. A cost-effectiveness analysis has been conducted for selpercatinib versus relevant comparators. As per the NICE reference case, cost-effectiveness is	The company has provided cost effectiveness results in the form of ICERs per QALY gained for the comparisons of selpercatinib versus (pseudo-control) docetaxel and versus

Parameter	Final scope issued by NICE	Decision problem addressed in the CS with company rationale where different to scope	EAG comment
	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 a NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies 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 who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	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. Proportional genetic testing costs will be included in the base case analysis of the submission but will be excluded as a scenario analysis as RET testing has become part of routine clinical practice due to the establishment of Genomic Hubs.[43,44] Despite their inclusion in the base case, the costs of RET testing are anticipated to be absorbed by the NHS.[43]	nintedanib+docetaxel.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • tumour histology (squamous or non-squamous) and • level of PD-L1 expression	The following subgroup analysis are considered: • Subgroup analyses in RET fusion-positive advanced NSCLC patients with brain metastases • PD-L1 status was not collected in the pivotal LIBRETTO-001 trial,[3] therefore subgroup analyses of patients based on PD-L1 expression were not able to be performed. In addition, the number of patients with RET fusion-positive, squamous NSCLC being treated in the second line was very low in the LIBRETTO-001 trial[3] and as such, any subgroup analyses conducted	Clinical advice to the EAG agrees that patients with brain metastases are a clinically important subgroup.

Parameter	Final scope issued by NICE	Decision problem addressed in the CS with company rationale where different to scope	EAG comment
		would not be statistically robust. Moreover, the presentation of subgroup analyses would not be in line with the Committee's expectation in TA760[1] that the prescribing practice in the NHS for patients with advanced, RET fusion-positive NSCLC would be the same regardless of squamous or non-squamous tumour histology.[1] For these reasons, subgroup analyses by tumour histology were not performed. Subgroup analyses were conducted in patients with brain metastases. It has been found that approximately 50% of patients with RET fusion-positive NSCLC experience brain metastases, therefore subgroup analyses in this population were performed.[45]	

AE=adverse event; BID=twice daily; CDF=Cancer Drugs Fund; DoR=duration of response; EAG=External Assessment Group; 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; MAIC=matching-adjusted indirect comparison; 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; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PSM=propensity score matching; PSS=Personal Social Services; QALY=quality adjusted life year; RET=rearranged during transfection; SACT=systemic anti-cancer therapy; TA=technology appraisal; TTD=time to treatment discontinuation
Source: Final scope issued by NICE and CS, Table 1

2.6.1 Population

As highlighted in Table 3, patients with RET fusion-positive NSCLC are unlikely to have squamous NSCLC and so the company has focussed its evidence on patients with non-squamous NSCLC.

In the TA760[1] Evidence Review Group (ERG) report, it was noted that the number of prior lines of treatment received by patients (median 2, range 1 to 15 [EMA,[39] Table 23]) and some types of prior treatment (multi-kinase inhibitors) received by LIBRETTO-001 trial[3] patients did not reflect the experience of NHS patients with NSCLC in the second-line setting. However, the NICE TA760[1] AC concluded that LIBRETTO-001 trial[3] results were generalisable to NHS patients with RET fusion-positive advanced NSCLC.

It was noted by the NICE TA760[1] AC that there was uncertainty around whether patients with RET fusion-positive NSCLC had a better prognosis than patients with other forms of NSCLC. The company (CS, p20) considers that:

> "While a positive RET fusion status may seem to be associated with improved prognosis compared to other forms of NSCLC, patients with RET fusion-positive NSCLC typically tend to be younger, have a non-smoking status and have a better tumour performance score than the general NSCLC population which may confound this association."

Clinical advice to the EAG agrees. Furthermore, as described in Section 2.3, meta-analysis[19] results suggest that RET fusions are more common in women than men, in younger people than in older people and in non-smokers than smokers, and that these differences were most strongly observed in people of Asian ethnicity. The LIBRETTO-001 trial[3] is a single-arm trial; evidence for comparators has not been examined specifically in patients with RET fusion-positive NSCLC. Therefore, when indirectly comparing the clinical effectiveness of selpercatinib versus comparators, it is important to adjust for prognostic factors, particularly age, ECOG performance status , sex, smoking status and ethnicity (see Section 2.6.3).

2.6.2 Intervention

The company has presented evidence for selpercatinib as per its EMA and MHRA conditional marketing authorisation for RET fusion-positive advanced NSCLC (see Section 2.5).

2.6.3 Comparators

The EAG agrees with the company (and the reasoning provided in Table 3) that the relevant comparators in this appraisal are:

- docetaxel
- nintedanib+docetaxel

Platinum doublet chemotherapy or immunotherapy may also be second-line treatment options for some NHS patients (Section 2.4). However, due to declining use of platinum doublet chemotherapy in the second-line setting and increasing use of immunotherapy in the first-line setting, the NICE TA760[1] AC concluded that these were not relevant comparators. Clinical advice to the EAG agrees that, in the NHS, platinum doublet chemotherapy and immunotherapy are used less frequently than docetaxel and nintedanib+docetaxel in the second-line setting.

Evidence for comparator treatments for patients with RET fusion-positive NSCLC is not available. In part, this is due to the relative rarity of RET fusions (see Section 2.3) but also because in trials where patients received docetaxel (e.g., the REVEL trial[46] and LUME-Lung 1 trial[42]) or nintedanib+docetaxel (LUME-Lung 1 trial[42]), patients were not tested for RET fusion-positive status. Therefore, the company's indirect treatment comparisons included comparator evidence from patients with NSCLC with other oncogenic drivers or unknown oncogene status. Utilising individual patient data (IPD), the company created a (pseudo-control) docetaxel arm by matching LIBRETTO-001 trial[3] patients and REVEL trial[46] docetaxel arm patients. The company then estimated treatment effects for selpercatinib versus (pseudo-control) docetaxel in the matched population. It was not possible to employ the same approach to compare selpercatinib versus nintedanib+docetaxel as the company did not have access to LUME-Lung 1 trial[42] IPD. NMAs were thus required to compare selpercatinib versus nintedanib+docetaxel.

The EAG has concerns about both the approach used and the success of matching when generating the (pseudo-control) docetaxel arm. Since the results from the comparison of selpercatinib versus (pseudo-control) docetaxel were used as inputs into the NMAs, the EAG also has concerns about the impact of using these data to generate NMA results. To explore the robustness of the company's NMA results, the EAG asked the company to conduct unanchored matching-indirect comparisons (MAICs) that only included data from the LIBRETTO-001 trial[3] and the LUME-Lung 1 trial[42] (clarification question A1). The LUME-Lung 1 trial[42] is the only published randomised controlled trial (RCT) designed to explore the clinical effectiveness of nintedanib+docetaxel as a second-line treatment for patients with advanced NSCLC (nintedanib+docetaxel versus placebo+docetaxel). Due to differences in important

patient characteristics that could not be adjusted for, and the lack of information about the methods used to generate unanchored MAIC results, the EAG cautions that these results may not be robust.

The EAG considers that results from the company's comparison of selpercatinib versus (pseudo-control) docetaxel, NMA results and unanchored MAIC results for all outcomes considered may not be robust (see Section 3.7).

2.6.4 Outcomes

Clinical advice to the EAG is that the outcomes listed in the final scope issued by NICE and reported by the company (see Table 3) are the most relevant outcomes for patients with RET fusion-positive NSCLC. Results for all these outcomes are available from the LIBRETTO-001 trial.[3] Clinical advice to the EAG is that outcomes for patients with brain metastases are also of interest to clinicians. The outcomes of CNS objective response rate (ORR) and CNS duration of response (DoR) were therefore additional outcomes measured for the subgroup of patients with CNS metastases.

The company generated ORR, PFS and OS results for selpercatinib versus (pseudo-control) docetaxel. The company also generated ORR, PFS and OS NMA results for the comparison of selpercatinib versus docetaxel and versus nintedanib+docetaxel. During the clarification process, the EAG asked the company to provide ORR, PFS and OS unanchored MAIC results for the comparison of selpercatinib versus docetaxel and versus nintedanib+docetaxel (clarification question A1). The EAG focussed on these three outcomes as ORR was the LIBRETTO-001 trial[3] primary outcome and PFS and OS are important outcomes that inform the economic analyses.

2.6.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 25-year period and costs were considered from an NHS and Personal and Social Services (PSS) perspective.

The cost effectiveness results presented in this report have been calculated using the confidential (Patient Access Scheme [PAS]) price of selpercatinib and list prices for all other drugs. Proportional genetic testing costs are included in the company base case analysis; results excluding this cost have been presented as a scenario analysis as RET testing has become part of routine NHS clinical practice due to the establishment of Genomic Hubs[43,44] and are anticipated to be absorbed by the NHS.[43] The company QALY shortfall analysis

results show that treatment with selpercatinib meets the criteria for a x1.2 severity weight; the company considers that a severity modifier of x1.7 should also be considered.

2.6.6 Subgroups

The company has carried out the following subgroup analysis: RET fusion-positive advanced NSCLC patients with brain metastases (results for this subgroup were not presented during TA760[1]). Clinical advice to the EAG is that patients with oncogenic drivers often present with or develop brain metastases in the course of their illness; patients with brain metastases often have worse outcomes, including worse HRQoL, than patients without brain metastases.

2.7 Other considerations

As highlighted by the company (CS, p26), if selpercatinib is recommended for use in the NHS after exit from the CDF, selpercatinib would remain the only targeted treatment available for patients with pre-treated, advanced RET fusion-positive NSCLC.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company in the CS. The key components are:

- direct evidence for selpercatinib (LIBRETTO-001 trial)
- indirect evidence for selpercatinib versus relevant comparators ((pseudo-control) docetaxel, docetaxel and nintedanib+docetaxel).

3.1 Critique of the methods of review(s)

Clinical effectiveness evidence was derived from a systematic literature review (SLR), originally conducted in September 2019 (SLR1), with subsequent updates in October 2020 (SLR2), July 2021 (SLR3) and January 2024 (SLR4). Full details of the methods used by the company to identify and select clinically relevant evidence of the efficacy and safety of treatments for advanced RET fusion-positive NSCLC who require systemic treatment are presented in the CS (Appendix D). The EAG considers that the company's SLR was sufficiently comprehensive and robust, although there are minor concerns regarding the data extraction and quality assessment procedures employed (see Table 4).

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1.2, Table 15.
Were appropriate sources searched?	Yes	CS, Appendix D.1.1.
Was the timespan of the searches appropriate?	Yes	CS, Section B.2.1.
Were appropriate search terms used?	Yes	CS, Appendix D.1.1, Table 1 to Table 12. Response to clarification question C4.
Were the eligibility criteria appropriate to the decision problem?	Yes	
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2.
Was data extracted by two or more reviewers independently?	Partially	It is stated in the CS, Appendix D.1.3 that data were extracted by a single reviewer and independently verified and validated by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix D.2.5.
Was the quality assessment conducted by two or more reviewers independently?	Yes	Two independent reviewers conducted quality assessment and a third reviewer conducted an independent quality check of the assessments (ERG TA760[1] report).
Were attempts to synthesise evidence appropriate?	Yes	In the absence of direct comparative evidence, the company provided results from NMAs and, during the clarification process, results from unanchored MAICs.

CS=company submission; EAG=External Assessment Group; MAIC=matching-adjusted indirect comparison; NMA=network meta-analysis; RCT=randomised controlled trial; SLR=systematic literature review
Source: LRiG in-house checklist

3.2 Critique of main trial of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

Given the expected paucity of studies available for comparator treatments in a RET fusion-positive patient population, the company's SLR inclusion criteria permitted the inclusion of RCTs and single-arm studies that enrolled patients with pre-treated NSCLC, rather than just pre-treated RET fusion-positive NSCLC. The company's SLR eligibility criteria also included several comparators that are not relevant to this appraisal. The company's SLR therefore identified 155 studies (428 records) that provided clinical effectiveness evidence of second- and later-line treatments for patients with pre-treated, advanced NSCLC.

Only the single-arm LIBRETTO-001 trial[3] provided directly relevant evidence of the clinical effectiveness of selpercatinib as a treatment for patients with pre-treated, advanced RET fusion-positive NSCLC. A second single-arm trial of selpercatinib as a treatment for patients with pre-treated, advanced RET fusion-positive NSCLC (LIBRETTO-321 trial[47]) was conducted in China. This study included fewer patients than the LIBRETTO-001 trial[3] and not all patients (34/47, 72.3%) had previously been treated with platinum-based chemotherapy; only ORR, DoR and safety outcome data are available from this trial.

The full list of studies included in the company's SLR is provided in CS, Appendix D.2.1, Table 16. In total, 145 RCTs and 10 single-arm studies were included in the company SLR. All 10 single-arm studies included patients with RET-altered tumours (CS, Appendix D.2.1, p41). Overall, 14 studies included patients with RET-altered tumours, suggesting that the company SLR included four RCTs of patients with RET-altered tumours; these four RCTs were not included in the company NMAs. In the company's factual accuracy check, the company clarified that this was because none of the trial publications reported any results for patients with RET-altered NSCLC. In addition, the company stated that in these four RCTs, RET testing was carried out retrospectively, the number of patients with RET alterations was small and all four of the RCTs studied vandetanib, which is not a relevant comparator for this appraisal.

To conduct NMAs, a docetaxel-pseudo trial arm was required; this arm was generated using data from the REVEL trial[46] (see Section 3.6.1 for details) The company NMAs included data from the LIBRETTO-001 trial[3] and 30 additional RCTs (see Section 3.6.2 and Appendix 3, Section 8.3, for details), including the REVEL trial.[46]

Given the relevant comparators for this appraisal are docetaxel and nintedanib+docetaxel, the EAG considers it is possible to carry out unanchored MAICs using data from only two trials, the LIBRETTO-001 trial[3] (selpercatinib data) and the LUME-Lung 1 trial[42] (placebo+docetaxel and nintedanib+docetaxel data). The EAG therefore asked the company to provide unanchored MAIC results (clarification question A1, see Section 3.6.3 for details).

3.2.2 Characteristics of the LIBRETTO-001 trial

The LIBRETTO-001 trial[3] is an ongoing, multicentre, international, open-label, phase I/II basket trial that enrolled patients with solid tumours treated with selpercatinib, including patients with NSCLC. The study is currently in phase II. In phase II of this trial, classification into cohorts was based on tumour type, type of RET alteration and prior treatment. Cohort 1 patients are relevant to this appraisal: RET fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy, including RET fusion-positive NSCLC.

The key characteristics of phase II of the LIBRETTO-001 trial[3] are summarised in Table 5.

Table 5 Key characteristics of phase I/II of the LIBRETTO-001 trial

Trial parameter	Description
Design	• Ongoing, multicentre, international, open-label, single-arm phase I/II trial • 85 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)
Patient population	• Patients with locally advanced or metastatic solid tumours 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 • No sudden deterioration 2 weeks prior to the first dose of selpercatinib
Treatment	• 160mg BID oral selpercatinib
Duration of study follow-up	• The first patient was treated on 9 May 2017 • The data cut-off that informed the EMA and MHRA regulatory submissions and TA760[1] was 16 December 2019 • The data cut-off used to inform this appraisal is 13 January 2023*
Primary outcome	• ORR based on RECIST v1.1 or RANO (dependent on tumour type), assessed by an IRC; median follow-up=[redacted] months
Secondary outcomes reported in the CS	• DoR; median follow-up=[redacted] months (IRC), [redacted] months (investigator) • CNS ORR; median follow-up=[redacted] months (IRC) • CNS DoR; median follow-up=[redacted] months (IRC) • PFS; median follow-up=[redacted] months (IRC), [redacted] months (investigator) • CNS PFS; median follow-up=[redacted] months (IRC) • OS; median follow-up=[redacted] months • HRQoL (EORTC QLQ-C30); median follow-up=[redacted] months • AEs; median follow-up=not reported

* As highlighted in the CS (p31), [redacted]

AE=adverse event; BID=twice daily; BOR=best overall response; CBR=clinical benefit rate; CNS=central nervous system; CS=company submission; DoR=duration of response; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; HRQoL=health-related quality of life; IRC=independent review committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RANO=response assessment in neuro-oncology criteria; RECIST=response evaluation criteria in solid tumours; RET=rearranged during transfection

Source: CS, Table 3, Table 5, Table 15, p62, Appendix L (Table 44 and Table 45), company response to clarification question A3, Table 6

3.2.3 Characteristics of LIBRETTO-001 trial patients

Descriptions of the LIBRETTO-001 trial[3] IAS and OSAS are presented in Table 6. All efficacy data are derived from patients in the IAS; all patients in the IAS had received prior treatment with platinum-based chemotherapy for NSCLC. Safety data are presented for patients in the IAS and OSAS; the OSAS includes all patients treated with selpercatinib, regardless of tumour type or line of treatment.

IAS efficacy data and OSAS safety data were also used to inform TA760.[1] Additional efficacy analysis sets for which results were presented in TA760,[1] but not in the CS for this current appraisal, were the Primary Analysis Set (PrAS), a subset of the IAS (see Table 6) and the Supplementary Analysis Set 2 (SAS2); SAS2 is a small analysis set (n<[redacted]) which consists of RET fusion-positive NSCLC patients who had received prior systemic therapy other than platinum-based chemotherapy. Safety data reported in TA760[1] were from the NSCLC SAS (pre-treated and treatment-naïve patients with RET fusion-positive NSCLC) and OSAS only, not the IAS as in the CS for this current appraisal.

The EAG considers that the analysis sets used by the company in the CS are the most relevant analysis sets for this appraisal. The EAG considers that the IAS is the most relevant data set for all outcomes, with data from the OSAS providing additional relevant safety data.

Table 6 LIBRETTO-001 trial phase II analysis sets

Analysis set	Analysis set description
PrAS, n=105	The first 105 RET fusion-positive NSCLC patients enrolled in phase I and phase II who met the following criteria: 1. evidence of a protocol-defined qualifying and definitive RET fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included 2. measurable disease by RECIST v1.1 by investigator assessment* 3. received ≥1 lines of prior platinum-based chemotherapy 4. received ≥1 doses of selpercatinib
IAS, n=[redacted]	Patients with RET fusion-positive NSCLC previously treated with platinum-based chemotherapy: • all PrAS patients plus patients who met PrAS criteria 1-4 who were enrolled after the 105th patient, as of data-cut date of 13 January 2023
OSAS, n=[redacted]	All treated patients: • patients treated with selpercatinib, regardless of tumour type or line of treatment, as of data-cut date of 13 January 2023

* Patients without measurable disease who were enrolled in phase I dose escalation were included in the PrAS
CS=company submission; IAS=Integrated Analysis Set; NSCLC=non-small cell lung cancer; OSAS=Overall Safety Analysis Set; PrAS=Primary Analysis Set; RECIST v1.1=Response Evaluation Criteria in Solid Tumours, Version 1.1; RET=rearranged during transfection
Source: CS, Table 10 and Figure 4

The baseline demographic and disease characteristics of the LIBRETTO-001 trial[3] IAS population are presented in Table 7 and Table 8. While the number of patients in the LIBRETTO-001 trial[3] at the 13 January 2023 data-cut was greater than the number at the 16 December 2019 data-cut (used to inform TA760[1]), the proportions of patients with each characteristic were similar at each data-cut. Clinical advice to the company and the EAG concurs with that of the NICE TA760[1] AC that baseline characteristics of patients in the LIBRETTO-001 trial[3] IAS population are similar to those of patients who would be treated in NHS clinical practice.

Table 7 Characteristics of LIBRETTO-001 trial IAS patients

Baseline characteristic	16 December 2019 data-cut (n=184)	13 January 2023 data-cut (n=[redacted])
Age, years		
Median (range)	62.0 (23 to 81)	61.0 (23 to 81)
Age group, n (%)		
18-44 years	26 (14.1)	[redacted]
45-64 years	89 (48.4)	[redacted]
65-74 years	54 (29.3)	[redacted]
≥75 years	15 (8.2)	[redacted]
Sex, n (%)		
Female	105 (57.1)	140 (56.7)
Race, n (%)		
White	86 (46.7)	[redacted]
Black	9 (4.9)	[redacted]
Asian	82 (44.6)	[redacted]
Other/missing	7 (3.8)	[redacted]
ECOG performance status, n (%)		
0	66 (35.9)	[redacted]
1	114 (62.0)	[redacted]
2	4 (2.2)	[redacted]
Smoking history, n (%)		
Never	125 (67.9)	[redacted]
Former	55 (29.9)	[redacted]
Current	4 (2.2)	[redacted]
Disease stage at diagnosis, n (%)		
I-II	4 (2.2)	[redacted]
III	10 (5.4)	[redacted]
IV	170 (92.4)	[redacted]
Time from diagnosis, months		
Median (range)	24.2 (1.5 to 164.8)	[redacted]
Primary NSCLC diagnosis, n (%)		
Adenocarcinoma	Not reported	221 (89.5)
History of metastatic disease, n (%)		
Yes	179 (97.3)	[redacted]
Time from diagnosis of metastatic disease, months, n (%)		
Median (range)	19.5 (1.0 to 108.1)	[redacted]
CNS metastasis at baseline by investigator, n (%)		
Yes	60 (32.6)	[redacted]

CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; IAS=integrated analysis set; NSCLC=non-small cell lung cancer
Source: EMA,[39] Table 21 and Table 22; CS, Table 6 and Table 7

Table 8 Prior treatments received by LIBRETTO-001 trial IAS patients

Prior treatment	16 December 2019 data-cut (n=184)	13 January 2023 data-cut (n=[redacted])
Type of prior systemic therapy, n (%)		
Platinum chemotherapy	184 (100)	[redacted]
Anti-PD-L1 therapy	100 (54.3)	[redacted]
MKI	67 (36.4)	[redacted]
Number of prior systemic regimens, n (%)		
1-2	101 (54.9)	[redacted]
≥3	84 (45.7)	[redacted]
Median (range)	2.0 (1 to 15)	[redacted]
Prior radiotherapy, n (%)		
Yes	103 (56.0)	[redacted]
No	81 (44.0)	[redacted]
Prior cancer-related surgery, n (%)		
Yes	84 (45.7)	[redacted]
No	100 (54.3)	[redacted]

IAS=integrated analysis set; MKI=multi-kinase inhibitor; PD-L1=programmed death-ligand 1
Source: EMA,[39] Table 23, CS Table 8, Company response to clarification question A4, Table 7

3.2.4 Quality assessment of the LIBRETTO-001 trial

The company conducted a quality assessment of the LIBRETTO-001 trial[3] using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies.[48] The responses to each quality item on the CASP[48] checklist are either, 'yes', 'no' or 'cannot tell'. The company's assessments and EAG comments are presented in Appendix 4, Section 8.4, Table 49. The EAG considers that the LIBRETTO-001 trial[3] is of good methodological quality and that the data are well-reported. However, the EAG highlights that the LIBRETTO-001 trial[3] is a single-arm trial and single-arm trials tend to be at single-arm trials tend to be at higher risk of selection bias and confounding than RCTs.

3.2.5 Statistical approach adopted for the analysis of the LIBRETTO-001 trial data

The LIBRETTO-001 is a single-arm study; no statistical hypothesis testing was performed. Information relevant to the statistical approach taken by the company has been extracted from the CS, CSR,[3] the most recent versions of the trial protocol[49] (version 9.0, dated 3 June 2020) and the trial statistical analysis plan (TSAP),[50] version 3.0, dated 19 December 2022). The EAG also referred to the Drilon 2019 publication[51] of the LIBRETTO-001 trial[3] for previous versions of trial protocol (version 8.0, dated 10 May 2019) and the trial statistical analysis plan (TSAP, version 1.0, dated 8 August 2019), both of which are available as a supplementary document to this paper. A summary of the EAG checks of the pre-planned statistical approach

used by the company to analyse LIBRETTO-001 trial[3] data is provided in Appendix 1, Section 8.1, Table 42. The methods used to present the data appear to be appropriate.

3.3 LIBRETTO-001 trial efficacy results

Efficacy results are presented in the CS (CS, Section B.2.6 and Appendix L.2). Except where stated, all results presented in this section relate to patients with pre-treated, advanced RET fusion-positive NSCLC participating in phase II of the LIBRETTO-001 trial[3] (IAS population).

3.3.1 Key efficacy results

Efficacy results presented in the CS have been generated using data from the 13 January 2023 data-cut, at which point (CS, Table 9):

- [redacted] of IAS patients were still receiving selpercatinib
- the most common reason for treatment discontinuation was disease progression ([redacted])
- many patients ([redacted]) had received treatment with selpercatinib beyond disease progression.

Results have been previously reported for the IAS population from three different LIBRETTO-001 trial[3] data-cuts. The key results from each data-cut, up to and including the latest 13 January 2023 data-cut, are presented in Table 9; additional results for the 13 January 2023 data-cut are presented in Appendix 2, Section 8.2.1 to 8.2.3. Where results are available, the data show that results appear to be improving with each additional data-cut. Unlike the 16 December 2019 data-cut, [redacted] by the 13 January 2023 data-cut.

Table 9 Summary of LIBRETTO-001 trial key results, different data-cuts

Outcome	16 December 2019 (n=184)	30 March 2020 (n=218)	15 June 2021 (n=247)	13 January 2023 (n=[redacted])
Tumour response				
Median duration of follow-up, months (IQR)	9.2 (5.6 to 13.9)	12.0 (7.4 to 15.9)	21.2 (16.6 to 26.0)	[redacted]
ORR by IRC, % (95% CI)	57.0 (49.0 to 64.0)	57.0 (50.0 to 64.0)	61.1 (54.7 to 67.2)	[redacted]
Median DoR, months (95% CI)	17.5 (12.1 to NE)	17.5 (12.1 to NE)	28.6 (20.4 to NE)	[redacted]
PFS				
Median duration of follow-up, months (IQR)	11.0	13.6	24.7	[redacted]
Median PFS, months (95% CI)	19.3 (14.0 to NE)	19.3 (16.5 to NE)	24.9 (19.3 to NE)	[redacted]
OS				
Median duration of follow-up, months (IQR)	-	-	26.4	[redacted]
Median OS, months (95% CI)	-	-	NE	[redacted]

CI=confidence interval; DOR=duration of response; IQR=inter-quartile range; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Source: Drilon 2023[52] data supplement and CS, p50, Table 14, Table 15, Table 16 and Table 17

The EAG notes the following differences between the IRC-assessed and investigator assessed results:

- [redacted] were observed for patients considered to have a complete response, partial response or stable disease; however ORR was [redacted] assessed by IRC or investigator (Appendix 2, Section 8.2.1, Table 43)
- the median DoR was notably [redacted] for patients classified as responding by IRC than by investigator (Appendix 2, Section 8.2.1, Table 44)
- [redacted] were observed for the number of patients considered to have disease progression largely as a result of a [redacted] number of patients censored by the IRC than investigator as a result of subsequent therapy/surgery without documented progressed disease; however median PFS was [redacted] assessed by IRC or investigator (Appendix 2, Section 8.2.2, Table 45).

3.3.2 Pre-planned subgroup efficacy analyses

The only pre-planned subgroup efficacy analyses were for IRC-assessed ORR. Results from the 13 January 2023 data-cut are presented in the CSR,[3] (Figure JZJA.5.13) for the following key characteristics: age, sex, ECOG performance status, smoking status, RET fusion gene, prior multi-kinase inhibitor (MKI) treatment, any metastatic disease, number of prior systemic

therapies, prior immunotherapy, prior anti-PD-1/PD-L1 therapy, prior MKI, CNS metastases status at baseline and type of RET molecular assay. In general, results were consistent with IAS population ORR results, even when the number of patients in a subgroup was very small (e.g., [redacted]); when the size of subgroups was small, CIs were wide. The only outlying subgroup result that included at least a quarter ([redacted]) of all IAS patients in each subgroup, was for the subgroup analysis by [redacted], where the ORR for [redacted] was much lower. The results for each of the subgroups in this analysis were:

[redacted]

3.3.3 Efficacy results for patients with CNS metastases

As reported in the CS (Section B.2.7), the prevalence of patients with brain metastases is "high" in patients with RET fusion-positive NSCLC. The pre-planned subgroup analyses (for ORR) included patients with and without CNS at baseline in the IAS population, as defined by the investigator (CSR,[3] Figure JZJA.5.13). These results were presented in the CSR[3] but not in the CS. The results were:

- history of CNS metastases (n=[redacted]): ORR=[redacted]; 95% CI: [redacted] to [redacted]
- no history of CNS metastases (n=[redacted]): ORR=[redacted]; 95% CI: [redacted] to [redacted]

Subgroup analyses reported in the CS (Section B.2.7) investigated the efficacy (PFS or CNS ORR only) of selpercatinib in subgroups of patients with RET fusion-positive NSCLC (regardless of treatment history) with CNS metastases, as follows:

- IRC-assessed PFS: patients with NSCLC (regardless of treatment history) with investigator assessed CNS metastases at baseline (n=[redacted]); of these [redacted] ([redacted]) had been previously treated and belonged to the IAS population (see CSR,[3] Section 5.2.6)
- IRC-assessed CNS ORR: patients with NSCLC (regardless of treatment history) with measurable CNS disease at baseline ([redacted]); of these [redacted] ([redacted]) had been previously treated and belonged to the IAS population (see CSR,[3] Section 5.2.6.3.1); CNS ORR results were also presented for even smaller subgroups of these subpopulations with and without prior radiotherapy (CS, Table 18)

The EAG considers that results for patients with previously treated RET fusion-positive NSCLC would have been more informative than results for patients with RET fusion-positive NSCLC regardless of treatment history. In patients with RET fusion-positive NSCLC with CNS metastases who had been previously treated (n=[redacted]), median PFS was [redacted] months (95% CI: [redacted] to [redacted]) after a median duration follow-up of [redacted] months (CSR,[3] Section 5.2.6.3); these PFS results were [redacted] than the results reported for patients with RET fusion-positive NSCLC regardless of treatment history ([redacted] months [95% CI: [redacted] to [redacted]; n=[redacted]).

The EAG considers that conclusions cannot be drawn from the CNS ORR results due to the small numbers of patients in these subgroups.

3.4 Patient reported outcomes from the LIBRETTO-001 trial

HRQoL data, measured using LIBRETTO-001 trial[3] PRO data, are presented in the CS (Section B.2.6.5 and Appendix L.1). HRQoL data were collected using the European Organisation for Research and Treatment of Cancer quality of life C-30 (EORTC QLQ-C30) questionnaire.[53] HRQoL was assessed at baseline and approximately every 8 weeks (approximately every other cycle) during the first year until cycle 13. It was then assessed every 12 weeks (approximately every third cycle) until the end of treatment (EOT) visit, and at follow-up visits after treatment discontinuation. As of the 13 January 2023 data-cut, [redacted] ([redacted]) of patients in the IAS population had completed a baseline assessment and ≥1 additional follow-up assessment.

The EORTC QLQ-C30 questionnaire consists of an overall health status/quality of life (QoL) subscale, five functional subscales (physical, role, cognitive, emotional, social) and nine symptom subscales (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). A minimal clinically meaningful difference in HRQoL ("improvement" or "worsening") measured by each of these subscales was defined as ≥10-point difference from the baseline assessment value for each patient, this definition is consistent with published oncology work.[54]

The company reported (CS, p61) that, [redacted] of previously treated advanced RET fusion-positive NSCLC patients had experienced [redacted] in quality of life across the period of treatment with selpercatinib as determined by QLQ-C30 subscales." However, the EAG notes (CS, Appendix L.1, Table 42) that, while a [redacted] proportion of patients reported an "improvement" rather than a "worsening" at most cycle visits, for most subscales, up to the final cycle (Cycle 49), this [redacted] of all patients who completed the assessment at that visit. For the cognitive functioning and diarrhoea subscales, at most cycle visits, [redacted] reported "worsening" rather than "improvement". As it is not known which patients reported an "improvement" and which patients reported a "worsening" at any given visit, it is only possible to conclude that, on occasion, [redacted]. The presented data suggest that [redacted] of patients at least [redacted] their HRQoL at every visit during treatment and at EOT.

The only additional HRQoL data presented in the CS (p61) are the mean change scores from baseline for the global QoL and five functioning subscales. The reported data show the mean

change score [redacted] from baseline to EOT, i.e., [redacted] in HRQoL. However, the change did not meet the criteria for a meaningful change for any of the subscales (all mean changes were [redacted]). Change scores for the symptom subscales were not reported.

3.5 Safety and tolerability results from the LIBRETTO-001 trial

LIBRETTO-001 trial[3] (13 January 2023 data-cut) safety and tolerability data are presented in the CS for the IAS and OSAS populations (CS, Section B.2.10). 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.[27]

3.5.1 Treatment duration and dosage

Nearly all ([redacted], [redacted]) patients in the IAS population received the proposed selpercatinib starting dose of 160mg BID. The mean (range) time on treatment was [redacted] ([redacted]) months. Although equivalent data are not reported for the OSAS population, it is noted (CS, p75) that the relative dose intensity was similar (IAS, median and mean: [redacted], and [redacted]; OSAS, median and mean: [redacted] and [redacted]). The proportion of patients requiring dose reductions due to AEs was similar in both the IAS ([redacted] and OSAS ([redacted] populations.

3.5.2 Summary of LIBRETTO-001 trial adverse events

A summary of LIBRETTO-001 trial[3] treatment-emergent adverse events (TEAEs) is presented in Table 10. AEs were defined as treatment emergent (TEAE) if they started on or after the date of the first dose of selpercatinib (Study Day 1). Treatment-related AEs (TRAEs) were defined as AEs that the investigator considered were related to treatment with selpercatinib. In both the IAS and OSAS populations, [redacted] patients experienced a TEAE and [redacted] patients experienced a TRAE. Grade 3 or 4 AEs and serious AEs (SAEs) were [redacted] but were much [redacted] linked to treatment with selpercatinib. Permanent discontinuation of selpercatinib due to TEAEs or TRAEs was relatively [redacted]. [redacted] fatal TEAE in the OSAS population was attributed to treatment with selpercatinib (there were [redacted] fatal TRAEs in the IAS population).

Table 10 Summary of LIBRETTO-001 trial adverse event data

Type of AE	IAS (n=[redacted])		OSAS (n=[redacted])	
	TEAEs n (%)	TRAEs n (%)	TEAEs n (%)	TRAEs n (%)
Any	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 AE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
Fatal AE	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; IAS=Integrated Analysis Set; OSAS=Overall Safety Analysis Set; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event
Source: CS, Table 31

Rates of the most common (≥15%) TEAEs were [redacted] between the OSAS and IAS populations, although fatigue, rash and abdominal pain were [redacted] in the OSAS population than in the IAS population (CS, Table 32). The most common AE in the IAS population was [redacted], which was experienced by [redacted] ([redacted], [redacted]) of patients with pre-treated RET fusion NSCLC (and [redacted] of all patients in the OSAS population: [redacted], [redacted]). As noted in Section 3.4, experience of diarrhoea had a notable negative impact on HRQoL.

The [redacted] (Table 11) were AEs of special interest (AEOSI): hypertension, alanine aminotransferase (ALT) increase, aspartate aminotransferase (AST) increase and electrocardiogram (ECG) QT prolonged (CS, Table 33). AEOSIs were identified a priori based on predictions from the RET-related literature, the preclinical toxicology programme and clinical experience with selpercatinib (CS, p79). A fifth AEOSI was hypersensitivity. While AEOSIs were [redacted], [redacted], and [redacted]. The company reported (CS, p74 and p79) that common TEAEs (including AEOSIs) were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication. Permanent discontinuation due to AEOSIs was [redacted].

Table 11 LIBRETTO-001 trial Grade 3 or 4 adverse events in ≥2% of patients

Type of AE	IAS (n=[redacted])		OSAS (n=[redacted])	
	TEAEs n (%)	TRAEs n (%)	TEAEs n (%)	TRAEs n (%)
≥1 Grade 3 or 4 AEs	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension*	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased*	[redacted]	[redacted]	[redacted]	[redacted]
AST increased*	[redacted]	[redacted]	[redacted]	[redacted]
ECG QT prolonged*	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

* Identified as an AE of special interest
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event
Source: CS, Table 33

Overall, the AE data showing similar frequencies of AEs in the IAS and OSAS populations suggest there are no unexpected AEs for patients with pre-treated RET fusion-positive NSCLC. Clinical advice to the EAG is that selpercatinib seems to have a manageable toxicity profile. The EAG highlights that as the LIBRETTO-001 trial[3] is a single-arm trial, the relative safety of selpercatinib versus comparator treatments cannot be determined from this source alone. See Section 3.8 for information on AEs related to comparator treatments (and similarities and differences when compared to the AEs experienced by patients in the LIBRETTO-001 trial[3]).

3.6 Company's indirect comparisons

The NICE TA760[1] AC considered that docetaxel and nintedanib+docetaxel were the relevant comparators to selpercatinib. The company's SLR did not identify any head-to-head trials investigating the effectiveness of selpercatinib versus either of these comparators and therefore conducted indirect comparisons. The company's preferred approach was to conduct NMAs. To include LIBRETTO-001 selpercatinib trial data in an NMA, it was necessary to generate a comparator pseudo-control arm. The company generated a (pseudo-control) docetaxel arm by conducting propensity score matching (PSM) using LIBRETTO-001 trial[3] selpercatinib IPD and REVEL trial[46] (patients with non-squamous disease only) placebo+docetaxel IPD (Section 3.6.1). These PSM data were then used in the company's NMAs (Section 3.6.2).

The EAG considered that, using LUME-Lung 1 trial[42] data, unanchored MAICs could also provide information about the relative effectiveness of selpercatinib versus docetaxel and versus nintedanib+docetaxel. Therefore, the EAG asked the company to carry out unanchored MAICs (clarification question A1). Details are provided in Section 3.6.3.

A summary of LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] study and baseline patient characteristics is presented in Appendix 4, Section 8.4, Table 47 and Table 48. The EAG considers that these trials are key because:

- the LIBRETTO-001 trial is the only study that provides selpercatinib evidence from the relevant population
- the company used REVEL trial[46] data to generate a (pseudo-control) docetaxel arm
- the LUME-Lung 1 trial[42] provides docetaxel and nintedanib+docetaxel evidence (the two relevant comparators); further, it is the only RCT that provides nintedanib+docetaxel evidence.

The main differences between trial inclusion criteria were that, unlike in the REVEL trial[46] and the LUME-Lung 1 trial,[42] all LIBRETTO-001 trial[3] patients:

- had RET fusion-positive NSCLC
- were permitted to have had more than one prior line of treatment for advanced NSCLC
- were permitted to have ECOG performance status 2.

A summary of the EAG's critique of the indirect evidence (selpercatinib versus (pseudo-control) docetaxel [Section 3.6.1], NMAs [Section 3.6.2] and unanchored MAICs [Section 3.6.3]), including the strengths and limitations of all three approaches, is presented in Section 3.7.

The EAG carried out a naïve comparison using LIBRETTO-001 trial[3] and LUME-Lung 1 trial[42] data; results show much higher ORR, median PFS and median OS in the LIBRETTO-001 trial[3] than in the LUME-Lung 1 trial[42] (Appendix 4, Section 8.5.1, Table 51).

3.6.1 Indirect evidence: selpercatinib versus (pseudo-control) docetaxel

Generation of the (pseudo-control) docetaxel arm

The (pseudo-control) docetaxel data were generated using PSM. As explained by the company (CS, Section B.2.9.1 and company response to clarification question A6), the aim of the company's PSM approach was to estimate the treatment effect of selpercatinib versus docetaxel, accounting for known differences in prognostic factors and treatment effect modifiers between LIBRETTO-001 and REVEL trial[46] populations. The factors and modifiers used in the company's PSM approach were validated as being clinically relevant by a UK expert clinician.

To conduct PSM, the company excluded [redacted] patients from the LIBRETTO-001 trial[3] IAS population; [redacted] patients had ECOG performance status 2 at baseline, [redacted] patients did not have non-squamous disease, and [redacted] patients had missing race data. Therefore, [redacted] patients from the LIBRETTO-001 trial[3] contributed data to the company's NMAs. In the REVEL trial,[46] 625 patients were allocated to the docetaxel arm and 618/625 received the randomised treatment. Approximately two thirds of these patients (447/618) were confirmed as having non-squamous disease and IPD data from this population were used to generate the (pseudo-control) docetaxel data.

Propensity scores were calculated using multivariable logistic regression. The company then estimated treatment effects for the matched population. The company did not account for RET fusion status in the PSM due to the "inconclusive prognostic nature of a RET fusion" (CS, p66) and because RET fusion status data were not collected as part of the REVEL trial[46] (company response to clarification question A8). The EAG highlights that the REVEL trial[46] did not actively recruit patients with RET fusion-positive disease and that RET fusions only occur in approximately 1% to 2% of the non-squamous NSCLC population.[13] Clinical advice to the EAG is that it is difficult to establish whether RET fusion status impacts treatment outcomes as RET fusions are more common in women than men, in younger people than in older people and in non-smokers than smokers.

Clinical advice to the company and the EAG is that the variables used in the PSM are clinically relevant prognostic factors and/or effect modifiers. Clinical advice to the EAG is that presence of CNS metastases is another important prognostic factor that may also be an effect modifier. However, the company PSM did not match for the presence of CNS metastases. The company

considered that matching for the proportion of patients with Stage IV disease would have accounted for differences in the percentage of CNS metastases (company response to clarification question A8).

Further, length of follow-up can affect results: REVEL trial[46] median OS follow-up is much shorter than LIBRETTO-001 trial[3] median OS follow-up (8.8 months in the docetaxel arm versus [redacted] months for patients treated with selpercatinib, respectively).

Matched covariates

The covariates that were matched as part of the PSM process are presented in Table 12. The EAG notes there were imbalances before and after PSM in the proportion of patients who were female, never smoked, were of Asian ethnicity and median time from diagnosis. As described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17,[55] there are methods that could have been used to improve overlap (i.e., trimming of the sample) or adjust for differences in patient characteristics in the PSM (i.e., multivariate regression on the matched sample). However, the company did not perform any further adjustments to account for any differences in patient characteristics that remained following matching between the selpercatinib and (pseudo-control) docetaxel arms.

Table 12 Summary of patient characteristics before and after matching

Baseline characteristic	LIBRETTO-001 trial (selpercatinib; n=[redacted])	REVEL trial	
		Before PSM (docetaxel; n=447)	After PSM[a] (docetaxel; n=234)
Age, mean, years	[redacted]	59.82	59.00
ECOG PS=1	[redacted]	68.3%	61.5%
Female	[redacted]	38.4%	46.2%
Never smoked	[redacted]	25.9%	48.3%
Race: Asian	[redacted]	14.2%	26.1%
Race: Other[b]	[redacted]	6.7%	11.1%
Stage III	[redacted]	8.9%	6.4%
Stage IV	[redacted]	86%	91.9%
Time since diagnosis to start of trial, median months	[redacted]	12.04	15.12

[a] The analysis followed greedy matching algorithm
[b] Race: 'Other' includes non-white, non-Asian and unknown
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; NSCLC=non-small cell lung cancer; NMA=network meta-analysis; PSM=propensity score matching
Source: CS, Table 19

Treatment effects for selpercatinib versus (pseudo-control) docetaxel arm

Company results for the comparison of selpercatinib versus (pseudo-control) docetaxel are presented in Table 13; these effect estimates were incorporated into the company's NMAs.

The results suggest [redacted] for ORR, PFS and OS.

Table 13 Estimated treatment effects for selpercatinib versus (pseudo-control) docetaxel

Endpoint	Relative effect (95% CI)
Objective response rate, OR	[redacted]
Progression-free survival, HR	[redacted]
Overall survival, HR	[redacted]

Note: the 95% CIs originally reported in the CS, Table 20, were incorrect
CI=confidence interval; HR=hazard ratio; OR=odds ratio
Source: company response to clarification questions A7 (Table 9) and clarification question C4 (Table 12)

3.6.2 Indirect evidence: network meta-analyses

Identification of studies for inclusion in the NMAs

As described in Section 3.2.1, the company's SLR identified 155 studies of second- or later-line NSCLC treatments, of these, 30 RCTs could be connected in at least one network of evidence to generate NMAs. The number of RCTs included in the networks for each outcome ranged from 17 to 26 (ORR, n=17; PFS, n=26; OS, n=25).

Each NMA included treatments that were not relevant to this appraisal. The EAG notes that there was only one RCT in addition to the studies included in the TA760[1] NMAs, namely the KEYNOTE-033 trial;[56] this trial only contributed evidence to the OS network of evidence. All trial data included in the NMAs were the most up to date available (company response to clarification question A9).

REVEL trial[46] patient data appear to have been included twice; the company network diagrams (CS, Figures 11 to 13) show a comparison between ramucirumab+docetaxel versus placebo+docetaxel (i.e., REVEL trial[46] data) and selpercatinib versus (pseudo-control) docetaxel (i.e., LIBRETTO trial data and a subset of patients already included in the NMA from the REVEL trial[46]).

NMAs: study characteristics

The company only provided limited information about the characteristics of the studies included in the NMAs, namely:

- trial name/study author(s)
- primary citation
- location
- intervention/comparator(s)
- outcomes which could contribute to NMAs (ORR, PFS, OS)
- subgroup data used (where applicable)

A summary of study characteristics is presented in Appendix 2, Section 8.3, Table 46. Overall, 16 RCTs included a docetaxel arm. Only the LUME-Lung 1 trial[42] included patients treated with nintedanib+docetaxel. The LUME-Lung 1 trial[42] comparator arm was placebo+docetaxel (henceforth referred to as docetaxel). All patients in the studies included in the NMAs had non-squamous NSCLC. It was noted in the TA760[1] ERG report that the median duration of study follow-up ranged from 7.1 months (ARCHER 1009 trial[57]) to 60.6 months (2008-GIRBA-1739 trial[58]); this variation may have introduced bias as results can become more (or less) favourable over time.

NMAs: patient characteristics

The company only presented LIBRETTO-001 trial,[3] the (pseudo-control) docetaxel arm and REVEL trial[46] docetaxel arm patient baseline characteristics. It is not known whether there were any important key baseline patient characteristic differences across the other included trials. As noted in Sections 2.3 and 2.6.1, patients with RET fusion-positive NSCLC are expected to have some characteristics that differ from those of patients with other forms of NSCLC.

The EAG has presented key LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] patient baseline characteristics (Appendix 4, Section 8.4.1, Table 48). These data show that:

- REVEL trial[46] and LUME-Lung 1 trial[42] baseline characteristics are broadly similar
- the LIBRETTO-001 trial enrolled proportionately [redacted] than the REVEL trial[46] or the LUME Lung-1 trial;[42] these characteristics are considered more common in patients with RET fusion-positive NSCLC
- the LUME-Lung 1 trial[42] included proportionately [redacted] patients who were diagnosed with Stage III NSCLC (particularly in the nintedanib+docetaxel arm) than in either the LIBRETTO-001 trial or in the REVEL trial[46]
- all patients in the REVEL trial[46] and in the LUME Lung-1 trial[42] received study drugs in the second-line treatment setting; in contrast [redacted] ([redacted]) LIBRETTO-001 trial patients were treated with selpercatinib in the third-line or later-line setting.

Quality assessment of the trials included in the NMAs

The EAG is satisfied that the methods employed by the company to assess the risk of bias of studies included in the SLR; for a full discussion, see Appendix 3, Section 8.3.2.

NMA methodology

The company performed ORR, PFS, and OS NMAs. In the ORR NMA, docetaxel appears to be a single node regardless of dose (60mg or 75mg); in the PFS and OS NMAs, docetaxel 75mg and 60mg doses have been included as separate nodes.

The trial ORR and PFS outcome data used as inputs into the company NMAs were consistently assessed by IRC. All NMAs were performed in the Bayesian framework, using random effects models and informative priors. For ORR, treatment effect estimates input into the NMAs were presented as odds ratios (ORs) with associated 95% CIs. For PFS and OS, the company used the methods described by Woods 2010[59] to perform HR NMAs. For studies that reported Kaplan-Meier (K-M) data but no HRs, the company digitised published K-M data and used the algorithm described by Guyot 2012[60] to generate pseudo-IPD. The company then estimated HRs and used these HRs in the NMAs. The EAG highlights that the NMA input values were not presented in the CS.

NMA treatment effect estimates were presented as ORs and HRs with associated 95% credible intervals (CrIs). The company's approach assumed that the proportional hazards assumption held; the company assessed the validity of the proportional hazards assumption for each study using the method described by Therneau and Grambsch.[61]

NMAs rely on the assumption of consistency, meaning that indirect evidence should be in line with direct evidence for each treatment comparison in each network of evidence. The company assessed inconsistency by comparing deviance information criterion (DIC) values for the standard network consistency model with an inconsistency model for each outcome.

The company performed meta-regression to investigate the impact of the following covariates on the estimated treatment effects:

- year of initial publication
- median age
- ECOG performance status; proportion ≥1
- male (%)
- Asian (%)
- level of PD-L1 expression (proportion ≥1% expression)
- RET fusion-positive tumours (%)

NMA results

The network diagrams for ORR, PFS and OS are presented in the CS (CS, Figure 11, Figure 12 and Figure 13, respectively). A summary of the company's NMA results is provided in Table 14. The company presented the results for comparisons versus selpercatinib. The results

suggest statistically significant treatment effects in favour of selpercatinib versus both comparators for ORR, PFS and OS.

Table 14 Relative treatment effect estimates from NMAs* for selpercatinib versus relevant comparators

Comparator	Treatment effect		
	ORR, pairwise median OR (95% CrI)	PFS, pairwise median HR (95% CrI)	OS, pairwise median HR (95% CrI)
Docetaxel	[redacted]	[redacted]	[redacted]
Nintedanib+docetaxel	[redacted]	[redacted]	[redacted]

* Random effects model with informative priors
CrI=credible interval; HR=hazard ratio; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Source: CS, p82

NMA results for the comparison of selpercatinib versus docetaxel were very similar to results for the comparison of selpercatinib versus (pseudo-control) docetaxel presented in Table 13.

In the CS (CS, Appendix D, Table 17), the company noted that the assumption of proportional hazards may not hold for 3/26 studies in the PFS NMA (CheckMate-057,[62] REVEL trial,[46] and ECOG-ACRIN 1512[63]) and for 2/27 studies in the OS NMA (CheckMate-057[62]and ECOG-ACRIN 1512[63]).

The company did not provide detailed results from the meta-regression analyses, stating only that "models related to age (for PFS and OS) and year of initial publication (OS) were the only models to converge" (CS, p72) and "the majority of baseline characteristics were not identified as significant" (CS, p73). During the clarification process, the EAG queried how it was possible to reach this conclusion if age was the only baseline characteristic to converge, precluding meta-regression for the other baseline characteristics. The company responded that "…the majority of baseline characteristics were not identified to be significant but acknowledge that the impact of between-trial heterogeneity in characteristics that did not converge is undetermined" (company response to clarification question A10).

The company provided inconsistency assessment results (DIC values for consistency and inconsistency models) in the CS (CS, Table 27). The company concluded that the PFS and OS NMAs may be affected by inconsistency of evidence as the DICs for inconsistency models for PFS and OS were [redacted] and [redacted] units lower, respectively, than for consistency models. For ORR, the DIC for the inconsistency model was [redacted] units lower than for the consistency model. Based on these results, the company considered that inconsistency was expected to impact the ORR NMA results to a lesser extent than it impacted PFS and OS NMA results. The company did not provide detailed results (i.e., treatment effect estimates and 95% CrIs) from

the inconsistency model; the EAG therefore considers the impact of this inconsistency on the company's NMA results is uncertain.

3.6.3 Indirect evidence: unanchored matching-adjusted indirect comparisons

Rationale behind the EAG request for unanchored MAICs

The EAG asked the company to carry out unanchored MAICs to explore the robustness of company NMA results because:

- the EAG considers that the PSM approach did not result in sufficiently balanced population characteristics (selpercatinib versus (pseudo-control) docetaxel)
- the networks of evidence for each outcome were large and included studies of many irrelevant comparators and this is likely to substantially increase clinical and methodological heterogeneity across the networks; the company acknowledges that convergence could only be determined for patient age and year of publication (company response to clarification question A10)

The EAG asked the company to conduct unanchored MAICs that only included data from the LIBRETTO-001 trial[3] (selpercatinib) and LUME-Lung 1 trial[42] (docetaxel and nintedanib+docetaxel). An unanchored MAIC requires the strong assumption that every prognostic factor and/or treatment effect modifier that is imbalanced between the two studies is accounted for in the analysis. To achieve this, the intervention population is re-weighted to match the comparator population in terms of prognostic factors and/or effect modifiers.

As the LIBRETTO-001 trial[3] and the LUME-Lung 1 trial[42] do not share a common comparator, the EAG asked the company to carry out unanchored MAICs using LIBRETTO-001 trial[3] IAS population data and LUME-Lung 1 trial[42] adenocarcinoma population data to compare selpercatinib versus docetaxel and versus nintedanib+docetaxel (clarification question A1). A key advantage of this approach is that LIBRETTO-001 trial[3] data can be both matched and adjusted so that LIBRETTO-001 trial[3] patient characteristics are similar to LUME-Lung 1 trial[42] adenocarcinoma population patient characteristics for key prognostic factors and/or effect modifiers, without the need to generate a pseudo-control arm.

Unanchored MAICs: study and patient characteristics

In the clarification response, the company did not present information about the prognostic factors and/or effect modifiers that were matched and adjusted, or how well baseline patient characteristics were balanced after this process. Nor did the company provide information about the effective sample size for each unanchored MAIC following this process. These are important limitations which make it impossible to assess the robustness of unanchored MAIC results.

In Appendix A, provided alongside the company's factual accuracy check, the company provided information about the prognostic factors and/or treatment effect modifiers adjusted for in each of the unanchored MAICs. The company adjusted for the following baseline characteristics: sex, age, smoking history, ECOG performance status and presence of brain metastases. The company also provided information about how comparable the data were in the LIBRETTO-001 trial[3] (selpercatinib) and in the LUME-Lung 1 trial[42] (docetaxel and nintedanib+docetaxel) before and after weighting for these characteristics. After weighting, the presented baseline characteristics appeared to be well balanced. The company also provided the effective sample size for each unanchored MAIC; the effective sample size was approximately n=[redacted] for each analysis.

The EAG considers that important prognostic factors and/or treatment effect modifiers were adjusted for, i.e., sex, age, smoking history, ECOG performance status and presence of brain metastases. However, information about other potentially important baseline characteristics that were adjusted for in the PSM (i.e., ethnicity and median time from diagnosis) was not provided. Also, as in the NMAs, it was not possible to adjust for RET fusion status, number of previous lines of treatment, or other important prognostic factors and/or treatment effect modifiers that may not have been considered. Unreported and unaccounted characteristics can be a source of residual bias. In line with DSU TSD 18,[64] the EAG considers that if evidence exploring residual bias cannot be provided, then any estimates or conclusions from unanchored MAICs should be heavily caveated by noting that the amount of bias (systematic error) in these estimates is unknown, is likely to be "substantial", and "could even exceed the magnitude of treatment effects which are being estimated."[64]

Unanchored MAICs: quality assessment of included trials

The company's completed quality assessment of the studies included in the SLR was provided in a Word document in a reference pack alongside the CS (Quality Assessments_April24.docx). LIBRETTO-001 trial[3] quality assessment results are presented in Appendix 4, Section 8.4.2, Table 49. The REVEL trial[46] and LUME-Lung 1 trial[42] risk of bias assessment results are presented in Appendix 4, Section 8.4.2, Table 50. The EAG considers that the LIBRETTO-001 trial[3] is of good methodological quality and that the data are well-reported. However, the EAG highlights that the LIBRETTO-001 trial[3] is a single-arm trial and single-arm trials tend to be at higher risk of selection bias and confounding than RCTs. The EAG considers that the REVEL trial[46] and LUME Lung-1 trial[42] were conducted to a good standard and were at low risk of bias. Both trials were double-blind and so were at low risk of bias for detection bias, unlike most of the studies included in the NMAs.

Unanchored MAICs: results

The company's unanchored MAIC and NMA HRs are presented in Table 15 (ORR), Table 16 (IRC-assessed PFS) and Table 17 (OS). For selpercatinib versus both comparators, the results showed that unanchored MAICs generated [redacted] ORs for ORR and [redacted] HRs for PFS and OS than the NMA results. The company considered that these results showed that the NMA approach generated conservative estimates of the relative treatment effects of selpercatinib versus both comparators (company response to clarification question A1).

Table 15 Relative treatment effect estimates for selpercatinib versus comparators for ORR

Comparator	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median OR (95% CI)	RE NMA model with informative priors, pairwise median OR (95% CrI)
Docetaxel	[redacted]	[redacted]
Nintedanib+docetaxel	[redacted]	[redacted]

CI=confidence interval; CrI=credible interval; MAIC=matching-adjusted indirect comparison; OR=odds ratio; ORR=objective response rate; RE=random effects.
Source: Company response to clarification question A1, Table 3

Table 16 Relative treatment effect estimates for selpercatinib versus comparators for PFS by IRC

Comparator	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median HR (95% CI)	RE NMA model with informative priors, pairwise median HR (95% CrI)
Docetaxel	[redacted]	[redacted]
Nintedanib+docetaxel	[redacted]	[redacted]

CI=confidence interval; CrI=credible interval; HR=hazard ratio; IRC=independent review committee; MAIC=matching-adjusted indirect comparison; OS=overall survival; PFS=progression free survival; RE=random effects.
Source: Company response to clarification question A1, Table 1

Table 17 Relative treatment effect estimates for selpercatinib versus comparators for OS

Comparator	Selpercatinib versus comparator	
	Unanchored MAIC, pairwise median HR (95% CI)	RE NMA model with informative priors, pairwise median HR (95% CrI)
Docetaxel	[redacted]	[redacted]
Nintedanib+docetaxel	[redacted]	[redacted]

CI=confidence interval; CrI=credible interval; HR=hazard ratio; MAIC=matching-adjusted indirect comparison; OS=overall survival; RE=random effects.
Source: Company response to clarification question A1, Table 2

In line with PFS and OS NMA results, PFS and OS unanchored MAIC results assume that the proportional hazards assumption holds. The company presented the results from the Schoenfeld residual plots over time and concluded that the proportional hazards assumption held for the PFS analyses (selpercatinib versus docetaxel and selpercatinib versus nintedanib+docetaxel) and for the OS analysis for selpercatinib versus nintedanib+docetaxel; however, there was evidence that the assumption of proportional hazards may not hold for the

OS analysis for selpercatinib versus docetaxel. The EAG agrees with the company interpretation of Schoenfeld residual plots.

3.7 EAG summary and comments on company indirect evidence

When performing all indirect comparisons, it was not possible to adjust for two potentially important baseline characteristics, namely RET fusion status and number of previous lines of treatment; adjustments for these characteristics were not possible because all LIBRETTO-001 trial[3] patients had RET fusion-positive NSCLC and all REVEL trial[46] patients had only received one previous line of treatment.

3.7.1 Selpercatinib versus (pseudo-control) docetaxel (PSM)

Strengths

- the EAG is satisfied that appropriate prognostic factors and/or effect modifiers were considered for the generation of the (pseudo-control) docetaxel arm

Limitations

- the EAG considers there were important imbalances remained after the generation of the (pseudo-control) docetaxel arm for important baseline characteristics (e.g., proportion of patients who were female, never smoked, were people of Asian ethnicity and median time from diagnosis)
- length of study follow-up can affect results: REVEL trial[46] median OS follow-up is much shorter than LIBRETTO-001 trial[3] median OS follow-up (8.8 months versus [redacted] months, respectively). This means that REVEL trial[46] data were much less mature than LIBRETTO-001 trial data;[3] PFS and OS outcomes improved with subsequent data-cuts for patients treated with selpercatinib but it is unknown if longer patient follow-up in the REVEL trial[46] would also have resulted in improved PFS and OS for patients treated with docetaxel

3.7.2 NMA comparisons of selpercatinib versus docetaxel and versus nintedanib+docetaxel

Strengths

- NMA results appear to be consistent with the selpercatinib versus (pseudo-control) docetaxel results
- NMA results appear to be consistent with unanchored MAIC results (selpercatinib versus docetaxel and versus nintedanib+docetaxel)

Limitations

- selpercatinib is linked to the networks of evidence via (pseudo-control) docetaxel; there are imbalances in key baseline patient characteristics between selpercatinib and (pseudo-control) docetaxel which could introduce bias and impact NMA results
- baseline characteristics were not provided for all 31 trials included in the networks; if baseline characteristics are not sufficiently similar, this could bias results

- median follow-up for the assessment of outcomes varied across trials; this may introduce bias as results can appear more (or less) favourable as longer follow-up data become available
- the company networks of evidence included studies of many irrelevant comparators; this is likely to substantially increase clinical and methodological heterogeneity across the networks
- data from patients in one study appear to have been included twice, i.e., patients treated with docetaxel in the REVEL trial;[46] it is not appropriate to include data from the same patients more than once in the same NMA
- the company concluded that there was evidence that the assumption of proportional hazards may not hold for three studies (PFS: CheckMate-057,[62] REVEL trial,[46] and ECOG-ACRIN 1512;[63] OS: CheckMate-057[62] and ECOG-ACRIN 1512[63])
- it was not possible for the company to conduct thorough explorations of heterogeneity for each network of evidence as there were insufficient data for most of the company's meta-regression models to converge
- the company identified evidence of inconsistency in the PFS and OS NMAs; the impact of inconsistency on the company's NMA results is uncertain.

3.7.3 Unanchored MAIC comparisons of selpercatinib versus docetaxel and versus nintedanib+docetaxel

Strengths

- using a smaller network (n=2 trials) is likely to reduce heterogeneity and reduces the need to generate a pseudo-control arm and means patients from the docetaxel arm of the REVEL trial[46] are not included twice
- the LUME-Lung 1 trial[42] was a double-blind trial
- the proportion of known prognostic factors and/or treatment effect modifiers which were adjusted for by the company were well balanced between treatment arms at baseline for each unanchored MAIC analysis
- unanchored MAIC results appear to be consistent with the selpercatinib versus (pseudo-control) docetaxel (generated via PSM) results
- unanchored MAIC PFS and OS results are similar to NMA PFS and OS results

Limitations

The company provided limited information about the methods used to carry out the unanchored MAICs, specifically:

- it is unclear whether some potentially important LUME-Lung 1 trial[42] and LIBRETTO-001 trial[3] baseline patient characteristics were well balanced across the treatment arms after matching and adjusting (e.g., ethnicity, median time from diagnosis and other potentially important prognostic factors and/or treatment effect modifiers which may not have been measured); imbalances in these characteristics could result in residual bias
- the company concluded that there was evidence that the assumption of proportional hazards may not hold for the selpercatinib versus docetaxel OS analysis
- company unanchored MAIC ORR results are very different from company selpercatinib versus (pseudo-control) docetaxel and from NMA ORR results

3.8 Safety of selpercatinib versus docetaxel and versus nintedanib+docetaxel

For information, a comparison of summary safety data (any AE, any drug-related AE, any Grade ≥3 AE, any AE leading to treatment discontinuation, any SAE, any fatal AE and any fatal AE related to treatment) from the LIBRETTO-001 trial[3] and LUME-Lung 1 trial[42] is presented in Appendix 5, Section 8.4, Table 52.

Of note, time on treatment was considerably longer for patients treated with selpercatinib in the LIBRETTO-001 trial[3] (median [range]: [redacted] [redacted] months) than in the LUME-Lung 1 trial[42] (docetaxel, median [range]: 3.0 [0.07 to 31.10] months; nintedanib+docetaxel, median [range]: 4.2 [0.10 to 41.53] months). Despite the differences in time on treatment in the two trials, there were [redacted] AEs leading to treatment discontinuation and death and [redacted] SAEs in the LIBRETTO-001 trial[3] than in the LUME-Lung 1 trial.[42]

Common AEs associated with selpercatinib, docetaxel and nintedanib+docetaxel are presented in Appendix 5, Section 8.4, Table 53. The following AEs were more common with docetaxel or nintedanib+docetaxel than selpercatinib:

- hypertension
- neutrophil count decreased
- white blood count decreased
- alopecia
- haemoglobin decreased
- febrile neutropenia
- thromboembolic events.

Less common with docetaxel than either nintedanib+docetaxel or selpercatinib were the following AEs:

- diarrhoea
- alanine aminotransferase increased
- aspartate aminotransferase increased
- nausea
- decreased appetite
- vomiting
- pyrexia.

Clinical advice to the EAG is that overall, the data from the LIBRETTO-001 trial[3] suggest that for most patients, selpercatinib is likely to be better tolerated than either docetaxel or nintedanib+docetaxel.

3.9 EAG clinical effectiveness conclusions

Selpercatinib evidence is derived from a single-arm phase II study: the LIBRETTO-001 trial.[3] All LIBRETTO-001 trial[3] patients had RET fusion-positive NSCLC (the relevant population). The EAG agrees with the company that this trial is of good methodological quality. Comparator (docetaxel and nintedanib+docetaxel) evidence was derived from studies that included patients with unknown RET fusion-positive NSCLC.

The company generated a (pseudo-control) docetaxel arm to allow selpercatinib to be included in NMA networks. The (pseudo-control) docetaxel arm was generated using PSM (REVEL trial[46] population docetaxel data and LIBRETTO-001 trial[3] population data). Whilst prognostic factors and/or treatment effect modifiers were matched, imbalances remained between treatment arms; these imbalances could lead to biased estimates of treatment effects. The EAG, therefore, has concerns that company selpercatinib versus (pseudo-control) docetaxel ORR, PFS and OS results may not be robust.

The company carried out ORR, PFS and OS NMAs and unanchored MAICs to compare the effectiveness of selpercatinib versus docetaxel and versus nintedanib+docetaxel. Overall, company indirect comparison results suggest that selpercatinib is superior to docetaxel and to nintedanib+docetaxel. However, it is not possible to quantify this difference due to the following areas of uncertainty:

- the effectiveness of comparator treatments in a population with RET fusion-positive disease is not known
- method-related limitations
- heterogeneity, including study follow-up (in particular the difference between the REVEL trial[46] and LIBRETTO-001 trial[3]) and line of treatment, which may over- or under-state relative treatment effects

The EAG is therefore not confident that any of the indirect comparison results should be used to inform decision making.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of selpercatinib as a treatment option for adults with previously treated advanced RET fusion-positive NSCLC. The two key components of the economic evidence presented in the CS are (i) a systematic literature review and (ii) a report of the company's de novo economic evaluation. The company provided an electronic copy of their economic model, which was developed in Microsoft Excel; an updated company model was made available to the EAG as part of the clarification response.

4.1 Company review of published cost effectiveness evidence

Selpercatinib is a first in class therapy for adults with advanced RET fusion-positive NSCLC; there are no published cost effectiveness studies of a selective RET kinase inhibitor in this population.

The company carried out a literature review to identify the utility, resource use and cost data to inform the design of the company model. The first search (SLR1) was undertaken in 2019 and this was subsequently updated in September 2022 (SLR2). Details of the strategies used by the company to identify utility/HRQoL and resource use/cost data as well as inclusion/exclusion criteria are provided in the CS (Appendix H). A complete list of HRQoL studies (n=37) identified by the searches is provided in Appendix H (Table 30) and a complete list of studies reporting resource use or cost data (n=56) is provided in Appendix I (Table 31).

4.2 EAG critique of the company's literature review

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 presented in Table 18.

Table 18 EAG appraisal of company review methods

Review process*	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Partial. The most recent search was carried out in September 2022
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?	Titles and abstracts were screened by one researcher; 10% of the titles and abstracts underwent a quality check conducted by a second independent researcher
Was data extracted by two or more reviewers independently?	Partial. Data were cross-checked by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	n/a
Was the quality assessment conducted by two or more reviewers independently?	n/a
Were attempts to synthesise evidence appropriate?	n/a

* The search strategy also identified thyroid cancer publications
EAG=External Assessment Group; n/a=not applicable
Source: LR*i*G in-house checklist

4.3 EAG conclusions regarding company systematic review methods of review(s)

The company searches were designed to identify data to inform the design of the company model. The EAG considers that the company search strategies were of good quality; however, in line with the company clinical effectiveness searches, a further search should have been carried out in January 2024 to ensure that all relevant studies were identified.

4.4 EAG summary and critique of the company's submitted economic evaluation

4.4.1 NICE Reference Case checklist and Drummond checklist

Table 19 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG 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	Partially. The NICE TA484[65] PF health state utility value was used to estimate the utility value for the PF state (0.713), which was derived from patients in the CheckMate 057 trial. The NICE TA760 PD health state utility value (0.628) was used and represents a 'midpoint' between PD utility values in the LIBRETTO-001 and CheckMate 057 trials
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

EAG=External Assessment Group; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[66] and EAG comment

Table 20 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Evidence for selpercatinib has been drawn from the single-arm, phase II LIBRETTO-001 trial.[3] No comparator data are available for patients with RET fusion-positive disease.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

EAG=External Assessment Group; NMA=network meta-analysis
Source: Drummond and Jefferson 1996[67] and EAG comment

4.4.2 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 dead. The structure of the company model is shown in Figure 1.

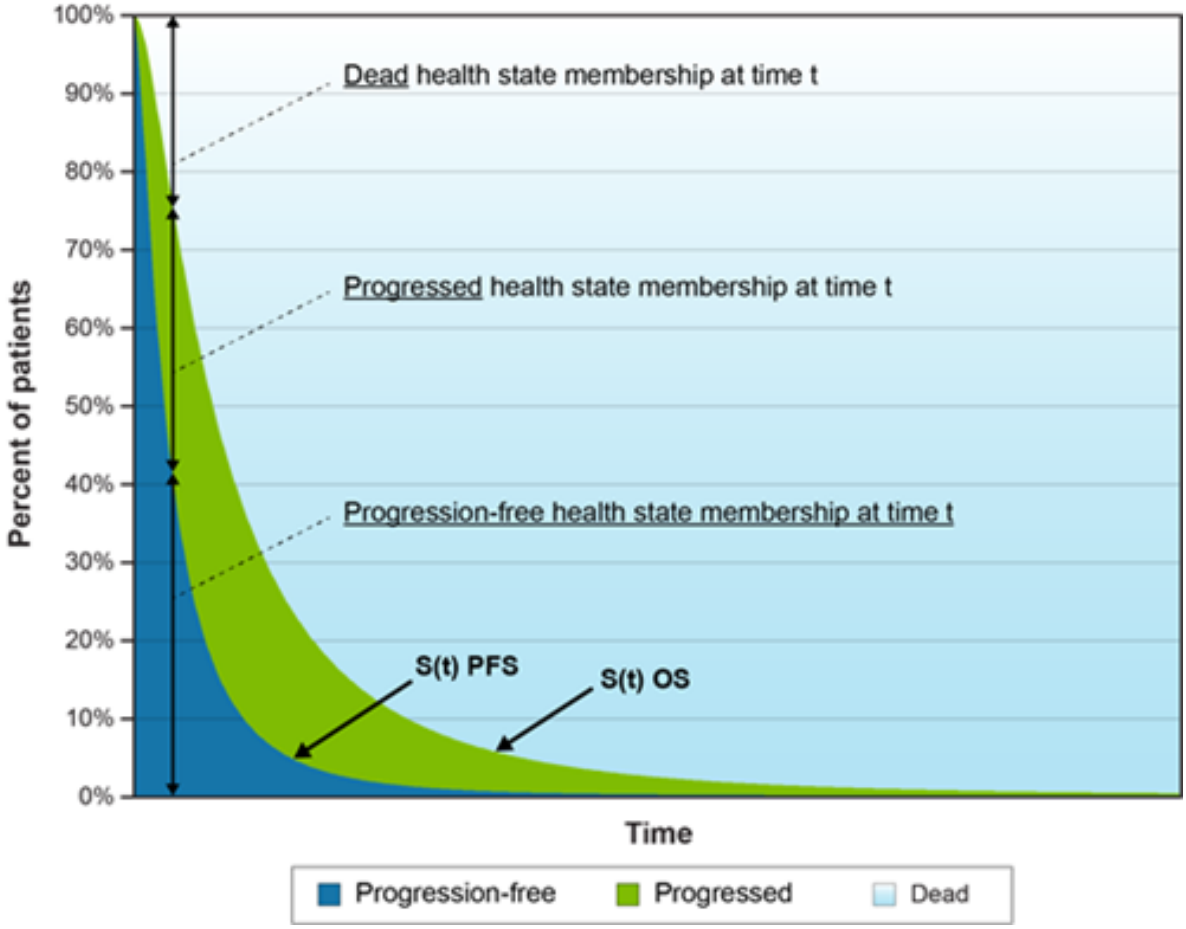

Figure 1 Structure of the company model

OS=overall survival; PFS=progression-free survival; S(t)=survival probability at time t
Source: CS, Figure 14

4.4.3 Population

The modelled population is adults with previously treated advanced RET fusion-positive NSCLC. The model baseline characteristics are based on LIBRETTO-001 trial[3] IAS population data (n=[redacted]).

The baseline characteristics of the modelled population are shown in Table 21.

Table 21 Modelled baseline patient characteristics

Model parameter	Value (SE)	Source
Mean age (years)	[redacted]	LIBRETTO-001 trial (IAS)
Percentage female (%)	[redacted]	
Mean weight (kg)	[redacted]	

IAS=integrated analysis set; SE=standard error
Source: CS, Table 36

4.4.4 Interventions and comparators

The modelled intervention and comparators are listed in Table 22. This table also includes information about the drug dosages and duration of treatment rules used in the company model.

Table 22 Model intervention and comparator treatments: second-line setting

Drug	Dosage	Duration of treatment
Selpercatinib	160mg twice daily (oral)	In 28-day cycles until disease progression or unacceptable toxicity
Docetaxel monotherapy	Docetaxel 75mg/m^2 on day 1 (IV)	Docetaxel: 21-day cycles until tumour progression or unacceptable AEs (max 4 cycles)
Nintedanib+docetaxel (whole population)	Nintedanib (oral) 200mg twice daily on days 2 to 21, in combination with docetaxel (IV) 75mg/m^2 on day 1	Docetaxel: 21-day cycles until tumour progression or unacceptable AEs (max 4 cycles) Nintedanib: until disease progression (max 6 cycles)

AE=adverse event; IV=intravenous
Source: CS, Table 35 and Table 53

4.4.5 Perspective, time horizon and discounting

The company states that, in line with the NICE Reference Case,[68] the perspective of the model is the NHS and Personal Social Services (PSS). The model cycle length is 1 week (no half-cycle correction implemented), the time horizon is 25 years, and costs and outcomes are discounted at 3.5% per annum.

4.4.6 Generating OS and PFS estimates

General approach employed by the company:

- **selpercatinib**: the company extrapolated LIBRETTO-001 trial OS, PFS and TTD data over the 25 year model time horizon; the numbers of patients contributing PFS and OS data were lower than in the IAS population (n=[redacted] and n=[redacted] respectively) to allow for creation of the (pseudo-control) docetaxel estimates
- **docetaxel**: the company created a (pseudo-control) docetaxel arm by adjusting REVEL trial[46] docetaxel IPD (see Section 3.6.1); the (pseudo-control) docetaxel data were extrapolated to generate (pseudo-control) docetaxel OS and PFS estimates over the 25 year model time horizon
- **nintedanib+docetaxel**: company OS and PFS NMA HRs were applied to the docetaxel OS and PFS estimates to generate nintedanib+docetaxel OS and PFS estimates

The process followed by the company to select the functions used to extrapolate LIBRETTO-001 trial[3] and (pseudo-control) docetaxel arm data was in line with the process outlined in NICE DSU TSD 14.[69] A range of standard parametric survival functions and flexible (spline) models were considered (n=19). For each treatment/outcome combination, the company assessed each function/model in terms of:

- statistical fit of functions/models to trial data based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores and tested the proportional hazards assumption between treatment arms
- goodness of fit of the functions/models to trial data based on visual inspection versus available K-M curves
- clinical plausibility of short-term and long-term survival estimates based on feedback from UK clinical experts[41] (and, for selpercatinib, published information from TA760[1]).

Overall survival

AIC and BIC scores were generated using regression models fitted to combined selpercatinib and docetaxel OS data. Based on AIC and BIC scores, the loglogistic and exponential functions ranked [redacted]. Clinical advice to the company was that the exponential distribution was the most appropriate function (CS, page 110). The company therefore generated OS estimates for selpercatinib, docetaxel and nintedanib+docetaxel using an exponential function.

Progression-free survival

AIC and BIC scores were generated using regression models fitted to combined selpercatinib and (pseudo-control) docetaxel PFS data.

Clinical advice to the company was that the loglogistic function (AIC: rank=[redacted]; BIC: rank=[redacted] was the most clinically plausible (resulting in [redacted]% of patients being progression-free at 20 years) (CS, p102). This function generated a median PFS value that aligned most closely with LIBRETTO-001 trial[3] data (LIBRETTO-001 trial[3] median PFS=[redacted] months; loglogistic function median PFS=[redacted] months). The company therefore chose to generate PFS estimates for patients treated with selpercatinib by using the loglogistic function.

Clinical advice to the company, based on landmark survival estimates, was that the spline knot 3 model (median PFS=[redacted] months; AIC: rank=[redacted]; BIC: rank=[redacted]; [redacted] of patients being progression-free at 20 years) generated the most clinically plausible estimates for patients treated with docetaxel or nintedanib+docetaxel (CS, p102).

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 (DCO: 13 January 2023). The generalised gamma distribution had the best statistical fit (AIC: rank=[redacted]; BIC: rank=[redacted]). Further, the interviewed clinical expert identified the generalised gamma extrapolation as the most clinically appropriate curve. The company therefore used the generalised gamma distribution to generate TTD estimates for patients treated with selpercatinib.

The company assumed that patients treated with docetaxel and nintedanib+docetaxel received the maximum length of treatment expected in clinical practice, namely:

- docetaxel: four treatment cycles (12 weeks)
- nintedanib+docetaxel: six treatment cycles (18 weeks), with docetaxel only being administered for four treatment cycles

4.4.7 Adverse events

The AE incidence data used in the company model are provided in the CS (Table 48). The AE data were obtained from the LIBRETTO-001 trial[3] (selpercatinib), the REVEL trial[46] (docetaxel) and the LUME-Lung 1 trial[42] (nintedanib+docetaxel). Grade ≥3 AEs with at least 2% difference in frequency between interventions were included in the model.

4.4.8 Health-related quality of life

Model health state utility values

The base case health state utility values used in the company model are shown in Table 23; these are the NICE TA760[1] Appraisal Committee preferred values.

Table 23 Base case health state utility values used in the company model

Model health state	Utility value (95% confidence interval)
Progression-free	0.713 (0.573 to 0.853)
Progressed disease	0.628 (0.665 to 0.712)

Source: CS, Table 51

Impact of adverse events on health-related quality of life

All AEs were assumed to occur during the first model cycle and last between 0 and 23.8 days (CS, Table 50). Utility decrements and AE durations were sourced from previous NICE TAs (including, TA428,[28] TA476[70] and TA484[65]) or based on assumptions. Utility decrements, AE durations and QALY losses are presented in the CS (Table 50).

4.4.9 Resources and costs

The following categories of costs were included in the company model (CS, Section B.3.5):

- intervention and comparator drug acquisition, drug administration and monitoring
- subsequent treatments
- medical management of the treatment (by health state)
- AEs
- end of life (terminal care) and genetic testing.

Drug acquisition costs

The drug acquisition list prices used in the company model were sourced from the BNF[71] and are presented in Table 24. Selpercatinib is available to the NHS at a confidential PAS price; this confidential price is used in all the company analyses. Nintedanib is also available to the NHS at a confidential PAS price; this confidential price is not known to the company.

Table 24 Drug acquisition costs (BNF 2023 list prices)

Drug	Form	Strength	Pack size	Cost per pack
Selpercatinib	Capsule	80mg	112	£8,736.00
Selpercatinib	Capsule	40mg	168	£6,552.00
Nintedanib	Capsule	100mg	60, 120	£2,151.10
Docetaxel	Vial	20mg/ml	8ml	£16.04

BNF=British National Formulary
Source: CS, Table 52

Selpercatinib is administered twice daily. During the LIBRETTO-001 trial,[3] patients received different doses of selpercatinib (160mg, 120mg, 80mg or 40mg). To account for different doses, the company created two treatment periods (model cycle 1 and model cycle 2 plus) and calculated selpercatinib acquisition costs based on the weighted average of LIBRETTO-001 trial[3] selpercatinib doses for two treatment periods (£[redacted] and £[redacted] respectively).

A relative dose intensity (RDI) multiplier can be used to reflect dose reductions and any treatment breaks. The LIBRETTO-001 trial[3] selpercatinib mean RDI for the NSCLC safety population (n=[redacted]) is [redacted]%. RDI values were not available for the comparator treatments and hence the company assumed that the RDI for all comparator treatments was [redacted]%.

In the base case, the company assumed drug wastage. For the oral drugs (selpercatinib and nintedanib), the cost of whole tablets was assumed wasted and for docetaxel (IV administration), it was assumed that unused content of an open vial was discarded.

Administration costs

The administration and monitoring costs used in the company model are provided in Table 25.

Table 25 Drug administration and monitoring costs

Treatment	Mean cost	Source/service code
Administration		
Selpercatinib	£11.00	TA520;[29] PSSRU 2022[72] Table 9 Band 6 hourly wage (12 minutes pharmacy time)
Docetaxel	£207.59	TA520;[29] NHS cost collection 2021/22[73] SB12Z outpatient (60 minute IV infusion)
Nintedanib+docetaxel	£218.59	TA520;[29] PSSRU 2022[72] Table 9 Band 6 hourly wage (12 minutes pharmacy time); NICE TA520;[29] NHS cost collection 2021/22[73] SB12Z outpatient (60 minute IV infusion)
Monitoring		
Oncologist visit (all interventions)	£221.48	NHS cost collection 2021/22,[73] NICE TA520[29]
ECG (7 required for selpercatinib only)	£222.62 per ECG	NHS cost collection 2021/22[73] (Outpatient – Medical Oncology Service)

ECG=electrocardiogram; IV=intravenous
PSSRU=Personal and Social Services Research Unit; TA=Technology Appraisal
Source: CS, Table 57

Subsequent treatments

Subsequent treatment costs were assumed to be independent of post-progression survival and were applied as a one-off cost on disease progression. The proportion of patients who accrued additional treatment costs due to receiving subsequent lines of treatment on progression to the 'progressed' health state and the duration of these treatment(s) were obtained from previous NICE Technology Appraisals (TA347[31] and TA520[74]). Subsequent treatments were categorised depending on whether the second-line treatment had been selpercatinib or chemotherapy. The pattern of subsequent treatments received by patients who had been treated with selpercatinib in the second-line setting was assumed to be the same as the treatments received by patients who had received atezolizumab in the second-line setting (TA520[74]). The cost estimates for the proportions of patients expected to receive each type of subsequent therapy after second-line treatment are presented in Table 26.

Table 26 Subsequent treatment costs

Drug	Mean cost per patient	Proportions of patients treated with each type of subsequent therapy	
		Selpercatinib	Chemotherapy*
Docetaxel	£858.27	14.9%	0.0%
Carboplatin	£1,187.33	8.7%	25.0%
Gemcitabine	£3,213.42	7.7%	7.7%
Erlotinib	£983.09	5.5%	5.5%
Pemetrexed	£4,125.75	4.9%	0.0%
Vinorelbine	£4,220.12	5.1%	5.1%
Radiotherapy	£11,989.97	55.0%	56.6%

* Chemotherapy represents docetaxel monotherapy or nintedanib+docetaxel
Source: CS, Table 58

Health state costs

The company model was populated with (inflated) medical resource use costs that were used in the company model that informed NICE TA520.[74] The per cycle cost for the progression-free health state was £167.90, whilst the per cycle costs for progressed disease health state was £155.04 (see CS, Table 59 for details).

Adverse event costs

The unit cost associated with each AE, and the source of each cost, are reported in the CS (Table 60). All the cost estimates were derived using information from previous NICE Technology Appraisals (TA428,[75] TA484,[65] TA516,[76] TA520,[74] TA621[77]), assumptions and NHS cost collection 2021/22.[73]

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 TA520.[29] The one-off end of life treatment cost used in the company model was £4,761.14 (see CS, Table 61 for details).

Cost of genetic testing for RET fusion status

The company has applied the proportional cost of [redacted] per tested patient. This cost was provided by NHS England during previous appraisals of selpercatinib as a treatment for RET fusion-positive NSCLC (TA760[1] and TA911[24]).

Severity modifier

The company used the severity modifier tool developed by SCHARR and Lumanity[78] to calculate absolute and proportional severity modifiers (Table 27). The company highlights that:

- shortfall results are very close to the threshold needed for the application of the 1.7x modifier
- patients with previously treated NSCLC have a considerable unmet need (LUME-Lung 1 trial[42] median OS results: nintedanib+docetaxel=10.1; docetaxel=9.1 months)
- NICE end of life criteria were met in the previous appraisal for selpercatinib in pre-treated RET+ NSCLC (TA760[1]), resulting in a willingness-to-pay threshold approximately equivalent to the application of a 1.7 x QALY modifier

The company therefore considers that a 1.7 x QALY modifier is appropriate versus both comparators and has applied this modifier when presenting economic analysis results.

Table 27 QALY shortfall analysis results

Drug	Docetaxel monotherapy	Nintedanib+ docetaxel
Expected remaining QALYs for the general population	[redacted]	[redacted]
Total QALYs that people living with the condition would be expected to have with current treatment	[redacted]	[redacted]
Absolute QALY shortfall	12.14	11.95
Proportional QALY shortfall	92.88	91.43
QALY weight	**1.2**	**1.2**

QALY=quality adjusted life year
Source: CS, Table 63

5 COST EFFECTIVENESS RESULTS

5.1 Base case incremental cost effectiveness analysis results

The EAG notes that nintedanib+docetaxel is only recommended by NICE (TA347[31]) as an option for the treatment of adenocarcinoma NSCLC histology; the primary diagnosis of 89.5% of the LIBRETTO-001 trial[3] IAS population was adenocarcinoma. The cost effectiveness results presented in Table 28 were generated using the company clarification model.

5.1.1 Probabilistic cost effectiveness results

Where data permitted, model parameter estimates were based on the uncertainty around the source data. Where data were not available to assess uncertainty, a user-defined percentage of the mean value as the standard error was applied. The model was run for 1,000 iterations.

Company pairwise probabilistic base case cost effectiveness analysis results using a 1.2 modifier and a 1.7 modifier are provided in Table 28 and fully incremental analyses are presented in Table 29.

Table 28 Company probabilistic pairwise base case results (selpercatinib PAS price)

Technologies	Total		Incremental		ICER/QALY	
	Costs	QALYs	Costs	QALYs	£/QALY*1.2	£/QALY*1.7
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	£53,102	£37,484
Nintedanib+docetaxel chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£47,567	£33,577
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	-	-

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life years
Source: company clarification model

Table 29 Company probabilistic fully incremental base case results (selpercatinib PAS price)

Treatment	Total costs	Total QALYs	ICER per QALY gained	
			1.2 severity modifier	1.7 severity modifier
Docetaxel	[redacted]	[redacted]		
Nintedanib+docetaxel	[redacted]	[redacted]	Extendedly dominated	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£53,102	£37,484

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life years
Source: company clarification model

The company pairwise and fully incremental deterministic base case cost effectiveness analysis results using a 1.2 modifier and a 1.7 modifier, are provided in the CS (CS, Table 69 and Table 67, respectively); these results are very similar to the company probabilistic results.

5.2 Deterministic sensitivity and scenario analyses

5.2.1 Sensitivity analyses

Company deterministic sensitivity analyses (no severity modifier applied) assessed the impact of changes to parameter values on base case analysis results; the impacts of the 25 most influential parameter changes on base case results are presented in the CS (Figure 26: selpercatinib versus docetaxel; Figure 27: selpercatinib versus nintedanib+docetaxel). For both comparators, the inputs that had the greatest impact on ICERs per QALY gained were the progression-free (PF) health state utility value for patients treated with selpercatinib and the rate used to discount costs and outcomes. The discount rate used in the company base case analysis was 3.5%; this rate is in line with the NICE Reference Case.[68]

5.2.2 Scenario analyses

For the comparison of selpercatinib versus docetaxel and versus nintedanib+docetaxel, the company has presented results from six scenario analyses (CS, Table 70: 1.7x modifier; CS, Appendix M: 1.2 x modifier). The scenario analyses involved using alternative approaches to generating selpercatinib PFS (stratified Gompertz and Weibull), OS (stratified lognormal and stratified Weibull) and TTD (PFS+14 weeks and TTD=PFS) estimates. Company results were most sensitive to using the stratified lognormal function to generate OS estimates and to assuming that TTD=PFS.

5.3 Model validation and face validity

The company took the following steps to validate model inputs and outputs:

- a thorough clinical validation process to inform choice of base case approaches to generating PFS, OS and TTD estimates
- verification of input data and coding by health economists not involved in the model development
- comparison of model clinical outcomes in the second-line setting with published outcomes for patients treated with selpercatinib, docetaxel and nintedanib+docetaxel

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The company model, developed in MS Excel, is designed to compare treatment with selpercatinib versus docetaxel and versus nintedanib+docetaxel for previously treated patients with RET fusion-positive advanced NSCLC. The company clarification response included an updated model; however, updated results tables were not provided. All EAG cost effectiveness results have been generated using the company clarification model.

6.1.1 CDF exit cost effectiveness analysis

The submitted model has addressed two of the issues raised by the Evidence Review Group (ERG) and NICE AC during TA760[1] (the appraisal of selpercatinib for this indication that led to selpercatinib being available via the CDF) by:

- generating selpercatinib treatment costs based on LIBRETTO-1 trial TTD data rather than using PFS as a proxy for TTD
- in absence of more robust data, using the progressed disease (PD) value of 0.628.

However, the issues relating to discounting and to the variation of utility values in the PSA remains, i.e., for some iterations utility in the PD health state is higher than in the PF health state (See Table 31).

The TA760[1] ERG's main concern was the relevance of the company's (pseudo-control) docetaxel data to the decision problem; this remains the EAG's main concern. The REVEL trial[46] data used by the company to generate the (pseudo-control) docetaxel arm data are the same as those used in TA760.[1] Further, the PSM process was unable to balance for RET fusion status, CNS metastases or line of treatment and, after matching, imbalances remained (female, patients who never smoked, people of Asian ethnicity and time since diagnosis) and these could bias selpercatinib versus (pseudo-control) docetaxel treatment effect estimates (Section 3.7.1).

The EAG highlights that:

- the REVEL trial[46] did not actively recruit patients with RET fusion-positive disease and, as RET fusion-positive disease only occurs in approximately 1% to 2% of all NSCLC cases,[13] REVEL trial[46] data cannot demonstrate the effectiveness of treatment with docetaxel on RET fusion-positive disease; this issue would remain even if it were possible to adjust for all prognostic factors and/or treatment effect modifiers
- REVEL trial[46] data (one prior treatment: 100%; median OS follow up=8.8 months) was compared with LIBRETTO-001 trial[3] data (≥2 prior treatments: [redacted]%; median OS follow up: [redacted] months)

For the comparison of selpercatinib versus docetaxel, the company has used (pseudo-control) docetaxel data; therefore, the EAG has consistently referred to (pseudo-control) docetaxel.

6.1.2 Model structure

The company model is much larger than it needs to be. It relies heavily on VBA code to produce deterministic and probabilistic results, and contains extraneous functionality associated with comparators (10 in total) and populations (4 in total) that are not of interest to this appraisal. Each of these elements contributes to the model being unnecessarily slow and cumbersome to run, which means it is difficult to review. There is no reason why VBA cannot be used to run a model if the code is sufficiently annotated and is used to increase efficiency; however, the company's VBA code was not annotated, and this made checking the algorithms problematic. Additionally, the model was built in such a way that it was not possible to simultaneously compare the live model outcomes for each treatment.

The EAG has checked that the parameter values in the CS match those used in the company model and were derived accurately from appropriate sources. The EAG has also checked the technical performance of the model using the TECH-VER checklist;[79] during the process of carrying out the checks, the EAG identified the error described in Table 30.

Table 30 Company model errors

Error	Issue and correction	Impact on the pairwise ICER for selpercatinib versus each comparator (no severity modifier)	
Including diagnostic testing costs in the PSA	The company has not included diagnostic testing costs in the PSA. The EAG has included diagnostic costs in the PSA.	versus docetaxel	+£1,000*
		versus nintedanib+ docetaxel	+£1,000*
Health state utility values in the PSA	The model PSA code allows utility values in the progression-free health state to be lower than the values used in the progressed health state. The EAG has revised the model so that progressed health state utility values are never higher than those for the progression free health state.	versus docetaxel	-£500*
		versus nintedanib+ docetaxel	-£500*
Nintedanib treatment costs continue to end of model time horizon	The company states in the CS (Section B.3.3.5) that it was assumed that nintedanib treatment would be received for a maximum of six cycles (18 weeks). In the model, nintedanib treatment costs are applied across the full model time horizon. The EAG has revised the model so that nintedanib treatment and administration costs stop after six cycles.	versus docetaxel	£0
		versus nintedanib+ docetaxel	+£4,582

* Reported as approximate (probabilistic) difference
CS=company submission; EAG=External Assessment Group; PSA=probabilistic sensitivity analysis

6.1.3 Summary of modelling checks/issues identified by the EAG

A summary of other modelling issues identified by the EAG is shown in Table 31.

Table 31 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company three-state partitioned survival model structure is appropriate; however, the EAG considers that the model structure is inflexible and change in parameter values has little effect on cost effectiveness results	6.1.2
Population	• The NICE TA760[1] AC accepted that the LIBRETTO-001 trial[3] data were generalisable to the NHS population with RET fusion-positive advanced NSCLC	n/a
Comparators	• The chosen comparators are appropriate; however, the EAG considers that (pseudo-control) docetaxel PFS and OS data are not robust	3.7
Survival modelling	• The EAG considers that the company to curve selection was not robust. However, EAG changes to the curve used to generate PFS results had limited impact on cost effectiveness results and the EAG is satisfied that the company approach to generating OS estimates was appropriate given the available clinical data and the limitations of the model structure	6.3
Utility values	• The company has used the utility values accepted by the NICE TA760[1] AC; no new HRQoL evidence has been submitted in this appraisal	n/a
Selpercatinib treatment costs	• The EAG has changed the model starting dose distribution to match the LIBRETTO-001 trial[3] IAS population starting dose distribution. • TTD may be overestimated. The EAG has investigated the impact on the cost effectiveness results of imposing a stopping rule at 10 years. Changes have only been made to costs; however, changes to treatment may affect outcomes. • The EAG has corrected the model so that nintedanib treatment and administration costs stop after six cycles (see EAG correction, Table 30)	6.1.2 and 6.4
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. The EAG has investigated the effect of revising the application of discounting and it made minimal difference to the cost effectiveness results in this instance, so no changes were made.	n/a
Subsequent treatment costs	• Subsequent treatment costs are appropriate	n/a
Healthcare resource use	• Healthcare resource use is appropriate	n/a
Adverse events	• Adverse event calculations and costs are appropriate	n/a

Aspect considered	EAG comment	Section of EAG report
Severity modifier	• The EAG and the company agree that a severity modifier of 1.2 is appropriate; however, the company has also presented a case for considering the use of a 1.7 multiplier	6.5
PSA	• See EAG corrections (Table 30)	6.1.2

AC=Appraisal Committee; EAG=External Assessment Group; HRQoL=health-related quality of life; IAS=integrated analysis set; NICE=National Institute for Health and Care Excellence; n/a=not applicable; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years; RET=rearranged during transection; TTD=time to treatment discontinuation

6.2 Relative treatment effect estimates

The comparator clinical effectiveness evidence presented by the company is not robust (see Section 3.7). The EAG considers that, without robust comparator data, it is not possible to generate robust cost effectiveness results.

Comparative of survival results are available for selpercatinib versus comparators:

- PSM: selpercatinib versus (pseudo-control) docetaxel
- NMA: selpercatinib versus (pseudo-control) docetaxel and versus nintedanib+docetaxel
- MAIC: selpercatinib versus docetaxel and versus nintedanib+docetaxel

The company used pseudo-control docetaxel data and NMA nintedanib+docetaxel results in the company model. No results were presented using MAIC results.

All subsequent sections of the economics critique should be considered with this in mind.

6.3 Survival modelling: selpercatinib versus (pseudo-control) docetaxel

The key survival modelling issue is the lack of flexibility in the structural relationship between selpercatinib and the comparators; it is not possible to fully explore how the relative effectiveness of selpercatinib versus (pseudo-control) docetaxel (or versus nintedanib+docetaxel) changes over time. This is because the model structure is based on the premise that, when comparing LIBRETTO-001 trial[3] and (pseudo-control) docetaxel PFS and OS data, the proportional hazards (or accelerated failure, in the case of accelerated failure time regression models) assumption holds and therefore it is appropriate to jointly fit different parametric distributions using treatment as a covariate. Choosing to generate survival estimates using the same distribution for patients treated with two different drugs means that, although the absolute effect of the two treatments varies depending on choice of distribution, the relative effect is assumed to remain fixed over the whole model timeframe.

It is not clear why the company used single regression models to estimate PFS and OS for selpercatinib and (pseudo-control) docetaxel. The company concluded that the proportional

hazard assumption held for selpercatinib versus (pseudo-control) docetaxel PFS yet chose to use different distributions to estimate PFS for the two treatments.

The company also concluded that there was evidence that the OS proportional hazards assumption may not hold for selpercatinib versus (pseudo-control) docetaxel yet chose to use the same distributions for both treatments. The company proportional hazard assumption assessments were carried out using LIBRETTO-001 trial[3] and data (company response to clarification question A1).

The EAG reached the same conclusions as the company regarding the validity of the PH assumption for selpercatinib versus (pseudo-control) docetaxel PFS and OS. Proportional hazard assessments were undertaken using reconstructed IPD based on selpercatinib and (pseudo-control) docetaxel K-M data presented in the model,

6.3.1 Progression-free survival

The company fitted parametric distributions (standard parametric and hazard spline [stratified and unstratified], n=19), with treatment as a covariate to selpercatinib and (pseudo-control) docetaxel data and generated joint AIC and BIC statistics for each of the 19 fitted distributions. The company considered that "…the statistical fit was relatively similar across all curve choices" (CS, p102). The company generated nintedanib+docetaxel PFS estimates by applying the company PFS NMA HR ([redacted], CS, Table 23) to the chosen (pseudo-control) docetaxel curve.

A company UK clinical expert considered that it was plausible that between [redacted] of patients treated with selpercatinib would be progression-free at 20 years and that the selpercatinib estimates generated by the loglogistic distribution were the most clinically plausible. The loglogistic distribution generated an estimate of [redacted]% of patients being progression-free at 20 years and a median PFS that closely aligned with LIBRETTO-001 trial[3] median PFS ([redacted] months and [redacted] months respectively). The company, therefore used the loglogistic distribution (AIC rank: [redacted]/19; BIC rank: [redacted]/19) to generate PFS estimates for patients treated with selpercatinib.

The company UK clinical expert considered that, based on landmark survival estimates, the spline knot 3 distribution (AIC rank: [redacted]/19; BIC rank: [redacted]/19) generated the most clinically plausible estimates for patients treated with docetaxel and nintedanib+docetaxel.

EAG approach to generating PFS estimates

EAG selpercatinib and (pseudo-control) docetaxel PFS estimates

The EAG considers that the company approach to distribution selection was subjective, arbitrary and open to significant bias. Using separate distributions to generate PFS estimates for patients treated with selpercatinib and (pseudo-control) docetaxel is technically incorrect, since the fit is assessed (i.e., AIC and BIC scores are produced) for distributions fitted to the combined data.

Additionally, the EAG considers that the company conclusion that the statistical fit of all considered distributions was similar is inaccurate as the differences between the highest and lowest ranking AIC and BIC scores are [redacted] points respectively. There is considerable support for models that are within 2 points of the model with the lowest score (Burnham 2004:[80] AIC; Schwarz 1978:[81] BIC). However, if the difference between the model with the lowest score and another model is >10 points, there is essentially no support for that model (AIC) or very strong evidence against the model (BIC).

Further, the EAG considers that the company should have given greater weight to visual fit when selecting the most appropriate distribution(s) to use to generate PFS estimates. The EAG highlights that, the loglogistic distribution, which was used by the company to generate PFS estimates for patients treated with selpercatinib, [redacted] (Figure 2).

The EAG considers that the spline knot 1 curve is a good statistical fit to the combined selpercatinib and (pseudo-control) docetaxel PFS data (AIC rank: [redacted]; BIC rank: [redacted]) and a better visual fit to selpercatinib PFS K-M data (Figure 2). This distribution is also a good visual fit to (pseudo-control) docetaxel data and generates 20-year PFS estimates for patients treated with selpercatinib that are in line with the company clinical expert estimate (Figure 2). Clinical advice to the EAG is that long-term PFS estimates for patients treated with selpercatinib are very uncertain.

Figure 2 Company and EAG selpercatinib and (pseudo-control) docetaxel PFS estimates
K-M=Kaplan Meier; PFS=progression free survival

EAG nintedanib+docetaxel PFS estimates

The EAG has retained the company approach to generating nintedanib+docetaxel PFS estimates by applying the company PFS NMA HR to the (pseudo-control) docetaxel curve; nintedanib+docetaxel PFS is therefore represented by a spline knot 1 curve.

6.3.2 Overall survival

The company considered that, given the relative maturity of LIBRETTO-001 trial[3] OS data (OS=[redacted]%, January 2023 data cut), statistical fit was important when choosing a distribution. The company chose the exponential distribution (AIC rank: [redacted]/19; BIC rank: [redacted]/19) to generate OS estimates for patients treated with selpercatinib and (pseudo-control) docetaxel and applied the company OS NMA HR ([redacted], CS, Table 25) to the (pseudo-control) docetaxel curve to generate OS estimates for patients treated with nintedanib+docetaxel. This choice was supported by clinical expert opinion. The EAG is satisfied that the exponential distribution is a reasonable fit to the selpercatinib and (pseudo-control) docetaxel K-M data, and that long-term estimates are plausible and in line with clinical expert opinion.

The company and EAG analyses suggest that the OS proportional hazards assumption may not hold for the comparison of selpercatinib versus (pseudo-control) docetaxel or versus nintedanib+docetaxel; this undermines the validity of some distributions. As an alternative to a proportional hazards model, the EAG has assessed the accelerated failure time assumption using selpercatinib and (pseudo-control) docetaxel OS K-M data from the company model and concluded that the accelerated failure time assumption holds. Since the exponential

distribution can be understood in both the proportional hazard and accelerated failure time frameworks, the EAG is satisfied that the exponential distribution is a reasonable choice. The EAG has not made any changes to the OS distribution for any treatment in the analysis.

6.4 Treatment costs

Selpercatinib baseline dose

The company model baseline distribution of selpercatinib doses does not match the LIBRETTO-001 trial[3] IAS population selpercatinib starting dose distribution (Table 32). This means that the mean baseline selpercatinib dose used in the cost effectiveness analysis is different to the one underpinning reported LIBRETTO-001 trial[3] patient outcomes. The EAG has adjusted the company model baseline dose distribution so that it matches the LIBRETTO-001 IAS population starting dose distribution. Since selpercatinib tablets are available to the NHS as 40mg and 80mg capsules, the EAG has rounded up the doses reported in the LIBRETTO-001 CSR to align with the next dose level that requires whole tablets.

Table 32 Selpercatinib starting dose

Dose	LIBRETTO-001 trial IAS population	Company model
20mg QD*	[redacted]	[redacted]
20mg BID	[redacted]	[redacted]
40mg BID	[redacted]	[redacted]
60mg BID	[redacted]	[redacted]
80mg BID	[redacted]	[redacted]
120mg BID	[redacted]	[redacted]
160mg BID	[redacted]	[redacted]
240 BID	[redacted]	[redacted]
Mean	[redacted]	[redacted]

BID=twice a day; IAS=integrated analysis set; QD=once per day
* Assumed 10mg BID for the mean calculation
Source: CSR, Table 14.1.1.2.1 and company model

Selpercatinib long-term treatment

Based on AIC/BIC statistics, visual fit and clinical advice, the company has chosen to use the generalised gamma distribution to estimate TTD for LIBRETTO-001 trial[3] patients treated with selpercatinib (AIC rank: [redacted]/10; BIC rank: [redacted]/10). The company's generalised gamma distribution fitted to LIBRETTO-001 trial[3] data resulted in [redacted] of patients receiving treatment for more than 10 years and [redacted] of patients receiving treatment for up to 20 years. NHSE advice to the EAG is that after an extended period (say, 10 years) of being progression-free, clinicians may discuss discontinuing selpercatinib treatment with patients; this may mean that, compared with NHS practice, the company's selpercatinib treatment cost may be an overestimate. The EAG has carried out a scenario analysis to investigate the potential impact on costs of stopping

treatment with selpercatinib at 10 years; this analysis does not include any potential impact on benefits.

Company selpercatinib treatment costs may also be overestimated if the approach to treatment beyond progression is different in the NHS than in the LIBRETTO-001 trial[3]. A substantial proportion of LIBRETTO-001 trial[3] patients ([redacted]; CS, Table 9) were treated with selpercatinib beyond IRC-assessed progression; median duration of treatment following progression lasted between 3.7 and 14.6 months depending on the patient subgroup.[82] Clinical advice to the EAG is that the proportion of LIBRETTO-001 trial[3] patients treated following progression and the length of time they were treated beyond progression would be unusual in the NHS. Advice to the EAG from NHSE is that it is common for a TKI to continue for a further 3 months until progression can be confirmed by a further CT scan.

Table 33 LIBRETTO-001 trial progression-free survival and time to treatment discontinuation

Rate (%)	Progression-free survival		Time to treatment discontinuation
	IRC-assessed	Investigator assessed	
≥12 months	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
≥36 months	[redacted]	[redacted]	[redacted]
≥48 months	[redacted]	[redacted]	[redacted]
≥60 months	[redacted]	[redacted]	[redacted]

IRC=independent review committee
Source: company clarification response, Table 16 and company model

(Pseudo-control) docetaxel and nintedanib+docetaxel

The company has assumed that patients treated with (pseudo-control) docetaxel and nintedanib+docetaxel receive the maximum length of treatment expected in clinical practice (docetaxel monotherapy: six treatment cycles [18 weeks]; docetaxel (with nintedanib): four treatment cycles [12 weeks]; nintedanib: six treatment cycles [18 weeks]). The EAG considers that this approach is appropriate. However, in the company model, patients treated with nintedanib+docetaxel were treated with nintedanib until disease progression. The EAG has revised the company model so that nintedanib treatment and administration costs stop after six cycles (see Table 30).

6.5 Severity modifier

The company short fall analysis generated absolute (proportional) shortfalls of 12.14 (92.88) and 11.95 (91.43) versus (pseudo-control) docetaxel and nintedanib+docetaxel, respectively (CS, Table 63). This translates to a QALY modifier of 1.2 versus both comparators (proportional shortfall: 0.85 to 0.95; absolute shortfall: 12 to 18).[68] The EAG considers that the company shortfall calculations are correct.

The company has presented cost effectiveness results using a 1.2 and a 1.7 multiplier. The company argues that it is appropriate to consider using a x1.7 modifier because:

- patients with previously treated NSCLC have a considerable unmet need (LUME-Lung 1 study OS: nintedanib+docetaxel: 10.1 months; docetaxel: 9.1 months)
- NICE End of Life criteria were met in the previous appraisal of selpercatinib in pre-treated RET fusion-positive advanced NSCLC ([1])

The EAG highlights that the NICE Reference Case[68] does not state that there is flexibility around the shortfall ranges that determine QALY weights.

6.6 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG has corrected the company base case and generated cost effectiveness results by making the following revisions presented in Table 34.

Table 34 EAG model revisions

Comparator	EAG revisions
(Pseudo-control) docetaxel	R1) Use spline knot 1 for PFS
	R2) Adjust selpercatinib starting dose
Nintedanib+docetaxel	R1) Use spline knot 1 for PFS
	R2) Adjust selpercatinib starting dose

PFS=progression-free survival

Details of EAG revisions to the company model are presented in Appendix 6, Section 8.6) of this EAG report. Deterministic cost effectiveness results for pairwise comparisons are provided in Table 36 and Table 38. Probabilistic cost effectiveness results for pairwise comparisons are presented in Table 37 and Table 39. Fully incremental analyses of probabilistic cost effectiveness results are presented in Table 40. All results have been generated using list prices for all drugs except for selpercatinib (PAS price). All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 35.

Table 35 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Selpercatinib	PAS
Nintedanib	PAS
Pemetrexed	CMU
All other drugs	eMIT (May 2024)

CMU=Commercial Medicines Unit; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme

Table 36 Deterministic pairwise results (selpercatinib versus (pseudo-control) docetaxel), PAS price for selpercatinib

EAG revisions	Selpercatinib		(Pseudo-control) docetaxel		Incremental		ICER		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	£/QALY *1.2	£/QALY *1.7
A1. Company base case (clarification model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,643**	**£53,869**	**£38,025**
A2. EAG corrected base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,643**	**£53,869**	**£38,025**
R1) Use spline knot 1 for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,609	£53,841	£38,005
R2) Adjust selpercatinib starting dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,584	£53,820	£37,990
B. EAG preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,549**	**£53,791**	**£37,970**
S1) Treatment discontinuation scenario & B1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,913	£48,261	£34,066

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALYs=quality adjusted life year

Table 37 Probabilistic pairwise results (selpercatinib versus (pseudo-control) docetaxel), PAS price for selpercatinib

EAG revisions	Selpercatinib		(Pseudo-control) docetaxel		Incremental		ICER		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	£/QALY *1.2	£/QALY *1.7
A1. Company base case (clarification model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£63,723**	**£53,102**	**£37,484**
A2. EAG corrected base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,370**	**£53,642**	**£37,865**
B. EAG preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,403**	**£53,669**	**£37,884**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 38 Deterministic pairwise results (selpercatinib versus nintedanib+docetaxel), PAS price for selpercatinib

EAG revisions	Selpercatinib		Nintedanib +docetaxel		Incremental		ICER		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	£/QALY *1.2	£/QALY *1. 7
A1. Company base case (clarification model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£60,641**	**£50,534**	**£35, 671**
A2. EAG corrected base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,223**	**£54,353**	**£38,367**
R1) Use Spline knot 1 for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,164	£54,303	£38,332
R2) Adjust selpercatinib starting dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,159	£54,299	£38,329
B. EAG preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,100**	**£54,250**	**£38,294**
S1) Treatment discontinuation scenario & B1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,938	£48,282	£34,081

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALYs=quality adjusted life year

Table 39 Probabilistic pairwise results (selpercatinib versus nintedanib+docetaxel), PAS price for selpercatinib

EAG revisions	Selpercatinib		Nintedanib +docetaxel		Incremental		ICER		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY	£/QALY *1.2	£/QALY *1.7
A1. Company base case (clarification model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£57,081**	**£47,567**	**£33,577**
A2. EAG corrected base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,123**	**£54,269**	**£38,308**
B. EAG preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,076**	**£54,230**	**£38,280**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 40 Company clarification base case probabilistic results (fully incremental analysis), PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained (1.2 severity modifier)
(Pseudo-control) docetaxel	[redacted]	[redacted]	
Nintedanib+docetaxel	[redacted]	[redacted]	Extendedly dominated
Selpercatinib	[redacted]	[redacted]	£53,102

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 41 EAG preferred base case probabilistic results (fully incremental analysis), PAS price for selpercatinib

Treatment	Total costs	Total QALYs	ICER per QALY gained (1.2 severity modifier)
(Pseudo-control) docetaxel	[redacted]	[redacted]	
Nintedanib+docetaxel	[redacted]	[redacted]	£46,861
Selpercatinib	[redacted]	[redacted]	£54,230

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

6.7 EAG cost effectiveness conclusions

The (pseudo-control) docetaxel comparator clinical effectiveness evidence presented by the company and all company indirect treatment comparison results may not be robust. The EAG considers that without robust comparator data, it is not possible to generate robust cost effectiveness results.

The company model structure is inflexible; this means that varying parameter values has little effect on cost effectiveness results and, therefore, EAG and company ICERs per QALY gained are similar.

The company has generated TTD estimates for patients treated with selpercatinib based on LIBRETTO-001 trial[3] TTD data. This approach results in some patients being treated in the PD health state for more than 3 months, and some patients in the PFS state being treated for 20 years. Clinical advice to the EAG is that, in the NHS, patients are unlikely to be treated for ≥3 months post progression and patients who remain progression-free will not be treated for 20 years.

The EAG and the company agree that a severity modifier of 1.2 is appropriate. However, the company has also presented a case for considering the use of a 1.7 multiplier.

In conclusion, the EAG considers that given the limitations of the comparator evidence base, the model structure and uncertainty around TTD for patients treated with selpercatinib, the company and EAG cost effectiveness results are unlikely to be robust.

7 REFERENCES

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8 APPENDICES

8.1 Appendix 1: Summary of pre-planned statistical approach used by the company to analyse data from the LIBRETTO-001 trial

A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the LIBRETTO-001 trial[3] is provided in Table 42.

Table 42 EAG assessment of statistical approaches used in the LIBRETTO-001 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations of phase II of the LIBRETTO-001 trial[3] are clearly defined in Table 10 of the CS and pre-specified (TSAP,[50] Section 2). Clinical effectiveness results are presented in the CS (Section B) for patients previously treated with platinum-based chemotherapy (IAS population) with safety analyses also presented for the OSAS population. The EAG considers these are the most appropriate populations for this appraisal.
Was an appropriate sample size calculation pre-specified?	Yes	As stated in the CS, Table 11, the total number of patients to be enrolled in Phase I depended upon the observed safety profile. The sample size required for the relevant cohort to this appraisal (Cohort 1: patients with RET fusion-positive solid tumours who have progressed on or are intolerant to standard first-line therapy for their cancers) is not presented in the CS but is pre-specified in the protocol[49] (Section 8.3). 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[3]
Were all protocol amendments made prior to analysis?	Unclear	Protocol changes were not summarised in the latest version of the protocol[49] (version 9.0) provided to the EAG during the clarification process. However, a summary of changes from version 1.0 to version 8.0 are provided in the supplementary document to the Drilon 2019 publication[51] of the LIBRETTO-001 trial.[3] 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 EAG considered that all these protocol amendments were appropriate and made prior to the 16 December 2019 data-cut that informed TA760[1].
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary outcome of phase II of the LIBRETTO-001 trial[3] is ORR (CS, Table 12) which was pre-defined (TSAP,[50] Section 3.1). Secondary efficacy outcomes of phase II of the LIBRETTO-001 trial[3] included DoR, PFS and OS (CS, Table 12), which were pre-defined (TSAP,[50] Sections 4.3.3, 4.3.9 and 4.3.10, 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,[50] Sections 10.2, 10.5, 10.7 and 10.8)

Item	EAG assessment	Statistical approach with EAG comments
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[3] was predefined as change from baseline in disease-related symptoms and HRQoL as measured by EORTC QLQ-C30 (protocol,[49] Section 8.1). The analysis approach is described in the CS (Section B.2.4, Table 12). The analysis population is defined in Section B.2.6.5 as patients in the IAS population in the "QLQ-C30 Analysis Set" (i.e., patients with RET fusion-positive NSCLC who had completed an EORTC QLQ-C30 baseline and at least one following assessment). The EAG 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[49] or TSAP.[50]
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were assessed and graded using the CTCAE Version 4.03[27] (CS, Section B2.10.1, p76). AEs were estimated as numbers and percentages of patients experiencing events; no formal statistical analyses of AEs were conducted. Summary data are presented in the CS (Section B.2.10) The EAG is satisfied that the approach employed was pre-defined (protocol,[49] 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,[3] except for imputation of partial dates (TSAP,[50] Section 4.1.2.1). DOR PFS and OS data were right-censored (CS, Table 11, TSAP[50] Sections 4.3.3, 4.3.9 and 4.3.10, respectively). The EAG agrees that it is appropriate not to conduct any data imputation and to present data as recorded
Were all subgroup analyses pre-specified?	Unclear	Prespecified subgroup analyses for ORR described in TSAP[50] Version 1.0 (Section 10.10) provided in the supplementary document to the Drilon 2019 publication[51] of the LIBRETTO-001 trial[3] were: age at enrollment (<65 years, ≥65 years); sex (male, female); race (white, Asian, other); ECOG performance status at baseline (0, 1–2); smoking status (never smoked, smoker); type of molecular assay (NGS on tumor or PCR, NGS on plasma, FISH); RET fusion gene (KIF5B, non-KIF5B, unknown); history of metastatic disease (yes, no); CNS metastasis at baseline by investigator (yes, no); number of prior systemic therapies (0, 1–2, ≥ 3); Prior anti PD-1/PD-L1 (yes, no); Prior multikinase inhibitor (yes, no). Results for all of these subgroup analyses are presented in the CSR[3] (Figure JZJA.5.13). The only subgroup analyses referred to in the latest version of the TSAP[50] Version 3.0 (Section 4.6.1) were for the safety and tolerability of selpercatinib and listed as: age at enrollment (<65 years, ≥65 years); sex (male, female); race (White, other). The only subgroup analyses reported in the CS were for PFS and CNS ORR for the following two subgroups: subgroups of patients with CNS metastases, defined by investigator (PFS) and subgroups defined by the presence of measurable disease (CNS ORR). It is unclear if these subgroups were prespecified. The outcomes for these subgroups do however appear to be post-hoc analyses.

AE=adverse event; CNS=central nervous system; CTCAE=common terminology criteria for adverse events; DoR=duration of response; EAG=External Assessment Group; 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; OSAS=Overall Safety Analysis Set; PFS=progression-free survival; PRO=patient reported outcome; RET=rearranged during transfection; TSAP=trial statistical analysis plan
Source: CS, CSR,[3] protocol versions 8.0[52] and 9.0[49] and TSAP versions 1.0[52] and 3.0[50]

8.2 Appendix 2: Additional efficacy results from the LIBRETTO-001 trial

8.2.1 LIBRETTO-001 trial tumour response results

A summary of selpercatinib ORR and DoR results (by IRC assessment) presented in the CS is provided in Table 43.

Table 43 Summary of LIBRETTO-001 trial tumour response results, IAS patients

Outcome	Assessed by IRC (n=[redacted])	Investigator assessed (n=[redacted])
Duration of follow-up (months)		
Median	[redacted]	[redacted]
Best overall response, n (%)		
Overall response	[redacted]	[redacted]
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Objective response rate, %		
ORR (95% CI)	[redacted]	[redacted]
Duration of response, months		
Median DoR (95% CI)	[redacted]	[redacted]

[a] Status as of the patient's last disease assessment on or before 13 January 2023
CI=confidence interval; IAS=integrated analysis set; IQR=interquartile range; IRC=independent review committee; NE=not evaluable; ORR=overall response rate
Source: CS, Table 14 and Table 15; CS, Appendix L.2, Table 43 and p130

8.2.2 LIBRETTO-001 trial PFS results

A summary of selpercatinib PFS results presented in the CS and CSR[3] is provided in Table 44.

Table 44 Summary of LIBRETTO-001 trial PFS results, IAS patients

PFS[a]	Assessed by IRC (n=[redacted])	Investigator assessed (n=[redacted])
Duration of follow-up (months)[b]		
Median (IQR)	[redacted]	[redacted]
Progression status, n (%)		
Disease progression	[redacted]	[redacted]
Death (no disease progression beforehand)	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Reason censored, n (%)		
Alive without documented disease progression	[redacted]	[redacted]
Subsequent therapy/surgery without documented PD	[redacted]	[redacted]
Discontinued from study without documented PD	[redacted]	[redacted]
Died or documented PD after missing ≥2 consecutive visits	[redacted]	[redacted]
Discontinued treatment and lost to follow-up	[redacted]	[redacted]
Duration of PFS, months[b,c]		
Median (95% CI)	[redacted]	[redacted]
Rate (95% CI) of PFS, %[b,d]		
≥6 months (95% CI)	[redacted]	[redacted]
≥12 months (95% CI)	[redacted]	[redacted]
≥24 months (95% CI)	[redacted]	[redacted]
≥36 months (95% CI)	[redacted]	[redacted]
≥48 months (95% CI)	[redacted]	[redacted]
≥60 months (95% CI)	[redacted]	[redacted]

[a] Status as of the patient's last disease assessment on or before 13 January 2023
[b] Estimated based on Kaplan-Meier method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% Confidence Interval was calculated using Greenwood's formula
CI=confidence interval; IAS=integrated analysis set; IQR=interquartile range; IRC=independent review committee; PFS=progression free survival
Source: CS, Table 16, Appendix L.2, Table 45, company response to clarification question C7 and LIBRETTO-001 trial CSR,[3] Table 14.2.4.1

8.2.3 LIBRETTO-001 trial OS results

A summary of selpercatinib OS results presented in the CS is provided in Table 45.

Table 45 Summary of LIBRETTO-001 trial OS results, IAS patients

OS[a]	**n=[redacted][a]**
Duration of follow-up (months)[b]	
Median follow-up (IQR)	[redacted]
Survival status, n (%)	
Dead	[redacted]
Censored	[redacted]
Duration of OS, months[b,c]	
Median (95% CI)	[redacted]
Rate (95% CI) of OS, %[b,d]	
≥12 months (95% CI)	[redacted]
≥24 months (95% CI)	[redacted]
≥36 months (95% CI)	[redacted]
≥48 months (95% CI)	[redacted]
≥60 months (95% CI)	[redacted]

[a] Status as of the patient's last disease assessment on or before 13 January 2023
[b] Estimated based on Kaplan-Meier method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% Confidence Interval was calculated using Greenwood's formula
CI=confidence interval; IAS=integrated analysis set; IQR=interquartile range; NE=not evaluable; OS=overall survival
Source: CS, Table 17

8.3 Appendix 3: Studies included in the company NMAs

8.3.1 Key characteristics of studies included in the NMAs

A summary of the key characteristics of the studies included in the company NMAs is presented in Table 46.

8.3.2 Risk of bias assessment of studies included in the NMAs

The company assessed the risk of bias of the RCTs using criteria recommended in the NICE Guide to the Methods of Technology Appraisal;[66] these methods are consistent with the methods recommended by the Centre for Reviews and Dissemination (CRD).[83] Single-arm studies were assessed using the CASP checklist for cohort studies.[48] The company's completed quality assessment of the studies included the company SLR was provided in a reference pack alongside the CS (filename: Quality Assessments_April24.docx).

The EAG is satisfied that the methods employed by the company to assess the risk of bias of studies included in the SLR; however, the company did not provide a narrative summary of the results of the risk of bias assessment exercise. The results of the risk of bias exercise were only reported in detail for SLR1 with the results from the risk of bias only reported overall for selection bias (randomisation, allocation and baseline prognostic factors), performance bias (blinding), attrition bias (unexpected imbalances in drop-outs) and detection bias (systematic differences between in how outcomes are determined). Reporting bias (evidence to suggest that the authors measured more outcomes than they reported) and whether an intention-to-treat (ITT) analysis was employed was only reported for SLR1.

The EAG highlights that most trials (23/31, 74.2%) included in the NMAs had an open-label design and were therefore at risk of detection and performance biases. However, the EAG is not concerned that any detection and performance biases arising due to lack of blinding would have had an important impact on NMA results.

Table 46 Key characteristics of the studies included in the company's NMAs

Trial	Location	Intervention	Comparator(s)	ORR	PFS	OS	Subgroup data used (where applicable)
LIBRETTO-001[3]	Multinational	Selpercatinib	(pseudo-control) docetaxel from REVEL	✓	✓	✓	matched selpercatinib and (pseudo-control) docetaxel
OAK[84]	Multinational	Atezolizumab	Docetaxel			✓	non-squamous
POPLAR[85]	Multinational	Atezolizumab	Docetaxel			✓	non-squamous
JAVELIN LUNG 200[86]	Multinational	Avelumab	Docetaxel		✓ [a, b]	✓[a]	non-squamous
AvaALL[87]	Japan	Bevacizumab+docetaxel	Docetaxel 60mg	✓	✓	✓	
TAILOR[88]	Italy	Erlotinib	Docetaxel		✓	✓	adenocarcinoma
NVALT-10[89]	Netherlands	Erlotinib	Erlotinib+docetaxel Erlotinib+pemetrexed	✓[c]	✓	✓[d]	non-squamous
INTEREST[90]	Multinational	Gefitinib	Docetaxel			✓ [e]	adenocarcinoma
V-15-32[91]	Japan	Gefitinib	Docetaxel 60mg		✓ [e]	✓ [e]	adenocarcinoma
CheckMate 057[62]	Multinational	Nivolumab	Docetaxel	✓	✓	✓[f]	
Checkmate 078[92]	Multinational	Nivolumab	Docetaxel	✓	✓[g]	✓	non-squamous
KEYNOTE-010[93]	Multinational	Pembrolizumab	Docetaxel		✓ [h]	✓ [h]	adenocarcinoma
KEYNOTE-033[56]	Multinational	Pembrolizumab	Docetaxel			✓[e]	
H3E-MC-JMEI[94]	Multinational	Pemetrexed	Docetaxel	✓[i]	✓	✓	non-squamous
LUME-Lung 1[42]	Multinational	Nintedanib+docetaxel	Docetaxel+placebo	✓	✓	✓	adenocarcinoma
I4T-JE-JVCG[95]	Japan	Ramucirumab+docetaxel	Docetaxel+placebo	✓	✓	✓	
REVEL[46]	Multinational	Ramucirumab+docetaxel	Docetaxel+placebo	✓ [a]	✓ [a]	✓ [a]	non-squamous
ECOG-ACRIN 1512[63]	USA	Erlontinib+cabozantinib	Erlontinib Cabozantinib	✓	✓	✓[j]	
ARCHER 1009[57]	Multinational	Dacomitinib	Erlotinib		✓	✓	adenocarcinoma

Trial	Location	Intervention	Comparator(s)	ORR	PFS	OS	Subgroup data used (where applicable)
WJOG 5108L[96]	Japan	Gefitinib	Erlotinib	✓[c]	✓		EGFR-negative
NCT00440414[97]	Greece	Pemetrexed	Erlotinib		✓[k]		non-squamous
CTONG0806[98]	China	Pemetrexed	Fefitinib	✓	✓	✓	
2008-GIRBA-1739[58]	Korea	Pemetrexed	Gefitinib	✓	✓[m]	✓[m]	non-squamous
Dai 2013[99]	China	Pemetrexed	Gefitinib	✓	✓[d]		
KCSG-LU08-01[100]	Korea	Pemetrexed	Gefitinib		✓		EGFR-negative
H3E-MC-S102[101]	Multinational	Pemetrexed+erlotinib	Pemetrexed	✓[c]	✓	✓	
H3E-MC-S103[102]	Multinational	Pemetrexed+erlotinib	Pemetrexed Erlotinib	✓	✓	✓	
NCT00950365[103]	USA	Pemetrexed+eErlotinib	Pemetrexed	✓	✓		
GOIRC 02/2006[104]	Italy	Pemetrexed	Pemetrexed+carboplatin		✓	✓	non-squamous
SUN1087[105]	Multinational	Sunitinib+erlotinib	Placebo+erlotinib		✓	✓	non-squamous
LUME-Lung 2[106]	Multinational	Nintedanib+pemetrexed	Placebo+pemetrexed	✓	✓	✓	

Note All studies included patients with non-squamous histology. All docetaxel doses are 75mg except where stated. Ticks in shaded cells indicate where there is evidence of non-proportional hazards
[a] Reported by subgroups in supplementary materials
[b] PFS only for a subgroup of PD-L1≥80% of non-squamous; not primary analysis set and will not connect to the network
[c] Derived from Table/Figure response data
[d] Must be derived from digitised KM curve
[e] Must be derived from forest plot
[f] Of note, OS for patients <1% PD-L1 violated proportional hazard, the group of PD-L1 ≥1% did not.
[g] CI must be derived from forest plot
[h] Pooled pembrolizumab dose
[i] Response in the primary paper (Hanna et al, 2004) is defined as ORR
[j] Cab vs Erl violate proportional hazards assumption but not Cab+Erl vs Erl
[k] Time to progression, not true PFS and may not be comparable
[m] Median and Ns will be used to calculate HR for non-squamous subgroup (adenocarcinoma + large cell carcinoma)
NMA=network-meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival programmed death-ligand 1
Source: CS, Appendix D.2.1, Table 16 and Table 17

8.4 Appendix 4: Key studies included in the company NMAs and unanchored MAICs

The key characteristics of the LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] are presented in Table 47. These three trials are considered to be the key studies by the EAG because:

- The LIBRETTO-001 trial is the only study for which evidence for selpercatinib was derived
- data from the REVEL trial[46] were used to generate the (pseudo-control) docetaxel arm
- the LUME-Lung 1 trial[42] provided evidence for both the relevant comparators to this appraisal (the LUME-Lung 1 trial[42] is the only RCT which has evidence for nintedanib+docetaxel).

Table 47 Key characteristics of the LIBRETTO-001, REVEL trial and LUME-Lung 1 trial

Trial	Design	Population	Relevant treatment	Length of follow-up
LIBRETTO-001	Ongoing, multicentre, international, open-label, phase I/II trial	• Patients 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 PS ≤2	Selpercatinib	Up to a median of [redacted] months for OS
REVEL	Multicentre, international, randomised, double-blind, placebo-controlled phase III trial	• Patients with pathologically confirmed, squamous or non-squamous stage IV NSCLC that had progressed during or after a single platinum-based chemotherapy regimen, with or without bevacizumab or maintenance therapy[a] • ECOG PS ≤1	Placebo +docetaxel[b]	Primary analysis: 8.8 months[b]
LUME-Lung 1	Multicentre, international, randomised, double-blind, placebo-controlled phase III trial	• Patients with histologically or cytologically confirmed stage IIIB/IV recurrent NSCLC (all histologies) who had received one previous chemotherapy[c] • ECOG PS ≤1	Placebo +docetaxel Nintedanib +docetaxel	Primary analysis: 7.1 months Final OS analysis: 31.7 months

[a] Only data from patients with non-squamous NSCLC were used to generate the (pseudo-control) docetaxel arm
[b] The intervention in this trial was ramucirumab+docetaxel; the median follow-up in this treatment arm was 9.5 months
[c] Only results from patients with non-squamous NSCLC (adenocarcinoma) were used in the NMAs
ECOG PS=Eastern Cooperative Oncology Group performance status; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

8.4.1 Baseline characteristics of the key studies

The baseline characteristics of the LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] are presented in Table 48.

Table 48 LIBRETTO-001 trial, REVEL trial and LUME-Lung 1 trial baseline characteristics

Baseline characteristic	LIBRETTO-001 trial IAS population	REVEL trial	LUME-Lung 1 trial adenocarcinoma population	
	Selpercatinib (n=247)	Docetaxel (n=447)[a]	Docetaxel (n=336)	Nintedanib+ docetaxel (n=322)
Age, years				
Median (range)	61 (23 to 81)	61 (25 to 86)	59 (30 to 80)	60 (29 to 80)
Age group, n (%)				
<65 years	[redacted]	304 (68.0)	240 (71.4)	232 (72.0)
≥65 years	[redacted]	143 (32.0)	96 (28.6)	90 (28.0)
Sex, n (%)				
Female	140 (56.7)	170 (38.0)	128 (38.1)	119 (37.0)
Race, n (%)				
White	[redacted]	353 (79.0)	253 (75.3)	253 (78.6)
Asian	[redacted]	64 (14.3)	78 (23.2)	65 (20.2)
ECOG performance status, n (%)				
0	90 (36.4)	140 (31.3)	99 (29.5)	96 (29.8)
1	150 (60.7)	306 (68.5)	237 (70.5)	225 (67.8)
2	7 (2.8)	0	0	1 (0.3)
Missing	0	1 (0.2)	0	0
Cigarette smoking history, n (%)				
Never	165 (66.8)	114 (25.5)	115 (34.2)	115 (35.7)
Disease stage at diagnosis, n (%)				
III	[redacted]	40 (8.9)	45 (13.4)	55 (17.2)
IV	[redacted]	384 (85.9)	237 (70.5)	215 (67.2)
Primary diagnosis, n (%)				
Adenocarcinoma	221 (89.5)	-	336 (100)	322 (100)
CNS metastasis at baseline, n (%)				
Yes	[redacted]	24/625 (3.8%)b	23 (6.8)	26 (8.1)
RET fusion-positive NSCLC				
Yes	[redacted]	Not reported	-	-

Baseline characteristic	LIBRETTO-001 trial IAS population	REVEL trial	LUME-Lung 1 trial adenocarcinoma population	
	Selpercatinib (n=247)	Docetaxel (n=447)[a]	Docetaxel (n=336)	Nintedanib+ docetaxel (n=322)
Type of prior therapy, n (%)				
Platinum chemotherapy	[redacted]	447 (100)	323 (96.1)	308 (95.7)
Taxane	[redacted]	110 (24.6)	65 (19.3)	77 (23.9)
Anti-PD-L1 therapy	[redacted]	-	-	-
MKI	[redacted]	-	-	-
Bevacizumab/VEGF/VEGFRi	[redacted]	86 (19.2)	-	-
Maintenance therapy	-	-	14 (4.2)	13 (4.0)
Number of prior systemic regimens, n (%)				
1	[redacted]	447 (100)	336 (100)	322 (100)
≥2	[redacted]	0	0	0

[a] Adenocarcinoma population
[b] Including patients with squamous NSCLC
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; IAS=integrated analysis set (subset of prior platinum chemotherapy); VEGF/VEGFRi=vascular endothelial growth factor/ vascular endothelial growth factor inhibitor
Source: CS Table 6, Table 7 and Table 8, CSR[3] Table 1.4 and company response to clarification question A4 (LIBRETTO-001); CS Table 19 and Paz-Ares 2017[107] data supplement (REVEL); TA347:[31] CS, Table 10 and ERG report, Table 3 (LUME-Lung 1)

8.4.2 Quality assessment of the key studies

The quality assessments of the LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] are presented in Table 49 and Table 50.

Table 49 Quality assessment of the LIBRETTO-001 trial

Quality assessment item	Company assessment	EAG comment
1. Did the study address a clearly focussed issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib in patients with advanced solid tumours including RET fusion-positive solid tumours. The primary endpoint of Phase I was MTD and/or the RP2D of selpercatinib. The primary endpoint of Phase II was ORR and secondary endpoints include DoR, PFS and OS.	Agree.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined in in the supplementary document to the Drilon 2019 publication[51] of the LIBRETTO-001 trial[3] and reported in CS, Table 5. However, it is an open-label, single-arm study, which could create selection bias.	Agree.

Quality assessment item	Company assessment	EAG comment
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.	Agree.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1 and assessed by an IRC. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.	Agree.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No. Confounding factors were not listed, however, baseline characteristics are extensively reported (see CS, Section B.2.3.3).	Agree. Clinical advice to the EAG is that the baseline characteristics reported include important prognostic, and therefore potentially confounding, factors.
5B. Have they taken account of the confounding factors in the design and/or analysis?	The study has no control arm, therefore randomisation or stratification are not applicable.	While confounding factors cannot be accounted for in the design of a single-arm trial, clinical advice to the EAG is that some important confounding factors were considered in subgroup analyses for ORR reported in the CSR[3] for the IAS. These included: age, sex, ECOG PS, smoking status, RET fusion gene, prior MKI treatment, any metastatic disease, number of prior systemic therapies, prior immunotherapy, prior anti-PD-1/PD-L1 therapy, prior MKI and CNS metastases status at baseline.
6A. Was the follow up of subjects complete enough?	Yes. Out of the [redacted] subjects enrolled in the treatment-exposed (IAS) cohort of LIBRETTO-001, a high proportion of patients ([redacted]) were continuing treatment at the latest data cut-off.[3]	Agree. At the 13 January 2023 data-cut, [redacted] ([redacted]) of IAS patients had been lost to follow-up and [redacted] had withdrawn consent (CSR,[3] Table JZJA.8.47).
6B. Was the follow up of subjects long enough?	The follow-up of subjects was long enough to collect a sufficient number of PFS and OS events and estimate the median for each of these outcomes.	Agree.
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked anti-tumour activity in previously treated patients with RET fusion-positive NSCLC, as illustrated by the ORR results.	Agree. However, the results cannot be directly compared against a comparator of interest.

Quality assessment item	Company assessment	EAG comment
8. How precise are the results?	The results were precise with RECIST assessment used on all scans to determine the ORR with an IRC. Response was confirmed by a repeat assessment no less than 28 days later.	The company has made no comment on the precision of the result estimates. The ORR, median PFS and median OS results could have been more precise as the range of the CIs for all these outcomes are relatively wide (upper CI not estimable for OS). As expected, subgroup results reported where there were few patients were also much less precise than results for larger sized subgroups.
9. Do you believe the results?	Yes. The primary endpoint for Phase II (ORR) aligns with published results from trials for other RET selective inhibitors.[108]	Agree the results align from results which have been previously presented for the ARROW trial[108-110] of prasletinib.
10. Can the results be applied to the local population?	Yes. These results can be applied to previously treated patients with RET fusion-positive NSCLC.	Agree.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other RET selective inhibitors.[108] ORR was 63.5% (n=148) in previously treated NSCLC patients who received pralsetinib in a Phase 1/2 trial compared to [redacted]% in the LIBRETTO-001 study.[109]	Agree. In patients who had received prior platinum therapy (n=136) as opposed to any prior treatment (n=158), the ORR was 59% and median PFS was 16.5 months in the most recent publication for the ARROW trial.[110]
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with RET-altered tumours in both first and subsequent lines of therapy.	The LIBRETTO-001 trial[3] results appear to be favourable for selpercatinib but the LIBRETTO-001 trial[3] does not provide direct comparative data versus relevant comparators necessary to inform decision making. Hence the need for indirect comparisons.

CI=confidence interval; CNS=central nervous system; CSR=Clinical Study Report; CTCAE=Common Terminology Criteria for Adverse Events; DoR=duration of response; EAG=Evidence Review Group; ECOG PS=Eastern Cooperative Oncology Group performance status; IAS=integrated analysis set; IRC=independent review committee; MKI=multi-kinase inhibitor; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; RECIST= Response Evaluation Criteria in Solid Tumours
Source: CS, Table 13

Table 50 Assessment of risk of bias conducted by company for the REVEL trial and LUME-Lung 1 trial

Criteria	REVEL trial	LUME-Lung 1 trial	EAG comment
Was randomisation carried out appropriately?	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Agree

Source: Word document (Quality Assessments_April24.docx) provided by the company with the CS

8.5 Appendix 5: Naïve comparisons of LIBRETTO-001 trial and LUME-Lung 1 trial results

8.5.1 Key efficacy results in the LIBRETTO-001 trial and LUME-Lung 1 trial

A summary of the key efficacy results in the LIBRETTO-001 trial[3] and the LUME-Lung 1 trial[42] is presented in Table 51.

Table 51 Summary of LIBRETTO-001 trial and LUME-Lung 1 trial key results, most recent data-cuts[a]

Outcome	LIBRETTO-001 trial IAS population[b]	LUME-Lung 1 trial adenocarcinoma population[c]	
	Selpercatinib (n=[redacted])	Docetaxel (n=336)	Docetaxel+ Nintedanib (n=320)
Tumour response			
IRC-assessed ORR, n (%)	[redacted]	12 (3.6)	15 (4.7)
PFS			
Median PFS, months	[redacted]	2.8	4.2
OS			
Median OS, months (95% CI)	[redacted]	10.3	12.6

[a] Most recent data-cut were 13 January 2023 for the LIBRETTO-001 trial[3] (median duration of follow-up [redacted] months for ORR to [redacted] months for OS) and 15 February 2013 for the [42] (median duration of follow-up 31.7 months at the time of the final OS analysis presented in TA347[31])
[b] Patients with RET fusion-positive NSCLC previously treated second-line or later following platinum-based chemotherapy (n=[redacted])
[c] Patients with adenocarcinoma treated second-line following prior chemotherapy, docetaxel (n=336) and nintedanib+docetaxel (n=320)
IRC=independent review committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival;
Source: CS, p50, Table 14, Table 15, Table 16 and Table 17 and results presented in TA347[31]

8.5.2 Adverse events in the LIBRETTO-001 trial and LUME-Lung 1 trial

A comparison of summary safety data from the LUME-Lung 1 trial[42] alongside data from the LIBRETTO-001 trial[3] is presented in Table 52. Common AEs associated with docetaxel and nintedanib+docetaxel alongside the equivalent data from the LIBRETTO-001 trial[3] are presented in Table 53. Of note, this table excludes the following AEs which were reported by [redacted] of patients treated with selpercatinib as Grade ≥3 AEs (see Table 11) because they were reported as any grade AEs by <5% of patients in either arm of the LUME-Lung 1 trial[42] adenocarcinoma population:

- hypertension
- hyponatraemia
- pneumonia
- ECG QT prolonged
- thrombocytopaenia
- lymphopenia.

The company reported the incidences of these AEs as Grade ≥3 AEs (from the LUME-Lung 1 trial[42] for nintedanib+docetaxel and the REVEL trial[46] for docetaxel) in the CS, Table 48.

Time on treatment was considerably longer for patients treated with selpercatinib in the LIBRETTO-001 trial[3] (median [range]: [redacted] [redacted] months) than the LUME-Lung 1 trial[42] (docetaxel, median [range]: 3.0 [0.07 to 31.10] months; nintedanib+docetaxel, median [range]: 4.2 [0.10 to 41.53] months).

Table 52 Adverse event summary from the LIBRETTO-001 and LUME-Lung 1 trials

Type of AE	LIBRETTO-001 IAS population[a]	LUME-Lung 1 adenocarcinoma population[b]	
	Selpercatinib n (%)	Docetaxel n (%)	Docetaxel+ nintedanib n (%)
Any	[redacted]	314 (94.3)	308 (96.3)
Any drug-related AE	[redacted]	241 (72.4)	260 (81.3)
Grade ≥3 AE	[redacted]	228 (68.5)	243 (75.9)
AE leading to treatment discontinuation	[redacted]	59 (17.7)	67 (20.9)
SAE	[redacted]	107 (32.1)	111 (34.7)
Fatal AE	[redacted]	32 (9.6)	56 (17.5)
Fatal AE related to treatment	[redacted]	1 (0.3)	6 (1.9)

[a] Patients with RET fusion-positive NSCLC previously treated second-line or later following platinum-based chemotherapy (n=[redacted])
[b] Patients with adenocarcinoma treated second-line following prior chemotherapy, docetaxel (n=336) and nintedanib+docetaxel (n=320)
AE=adverse event; IAS=Integrated Analysis Set; NSCLC=non-small cell lung cancer; RET=rearranged during transfection
SAE=serious adverse event; TEAE=treatment emergent adverse event; TRAE=treatment-related adverse event
Source: CS, Table 31; data reported in TA347[31]

Table 53 Comparison of most common AEs associated with docetaxel or nintedanib+ docetaxel versus selpercatinib[a]

AEs	LIBRETTO-001 IAS population[b]		LUME-Lung 1 adenocarcinoma population[c]			
	Selpercatinib		Docetaxel		Nintedanib+docetaxel	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
ALT increase	[redacted]	[redacted]	31 (9.3)	3 (0.9)	121 (37.8)	37 (11.6)
AST increase	[redacted]	[redacted]	24 (7.2)	2 (0.6)	97 (30.3)	13 (4.1)
Diarrhoea	[redacted]	[redacted]	82 (24.6)	12 (3.6)	139 (43.4)	20 (6.3)
Dyspnoea	[redacted]	[redacted]	52 (15.6)	20 (6.0)	54 (16.9)	15 (4.7)
Neutropenia	[redacted][d]	[redacted]	51 (15.3)	45 (13.5)	44 (13.8)	38 (11.9)
Fatigue	[redacted]	[redacted]	98 (29.4)	14 (4.2)	99 (30.9)	15 (4.7)
Vomiting	[redacted]	[redacted]	41 (12.3)	2 (0.6)	62 (19.4)	4 (1.3)
Nausea	[redacted]	[redacted]	59 (17.7)	2 (0.6)	91 (28.4)	3 (0.9)
Constipation	[redacted]	[redacted]	39 (11.7)	1 (0.3)	22 (6.9)	0 (0.0)
Decreased appetite	[redacted]	[redacted]	52 (15.6)	5 (1.5)	75 (23.4)	4 (1.3)
Pyrexia	[redacted]	[redacted]	47 (14.1)	1 (0.3)	39 (12.2)	2 (0.6)
Cough	[redacted]	[redacted]	63 (18.9)	2 (0.6)	42 (13.1)	3 (0.9)
Stomatitis	[redacted][d]	[redacted]	26 (7.8)	1 (0.3)	36 (11.3)	4 (1.3)
Alopecia	[redacted][d]	[redacted]	68 (20.4)	0 (0.0)	56 (17.5)	1 (0.3)
Neutrophil count decrease	[redacted][d]	[redacted]	135 (40.5)	116 (34.8)	131 (40.9)	116 (36.3)
Haemoglobin decrease	[redacted][d]	[redacted]	46 (13.8)	7 (2.1)	35 (10.9)	3 (0.9)
WBC decrease	[redacted]	[redacted]	94 (28.2)	61 (18.3)	89 (27.8)	63 (19.7)
Febrile neutropenia[e]	[redacted]	[redacted]	6 (1.8)	6 (1.8)	18 (5.6)	18 (5.6)
Thromboembolic events[f]	[redacted]	[redacted]	18 (5.4)	11 (3.3)	17 (5.3)	8 (2.5)

[a] Most common AEs defined as those occurring in ≥5% of patients in either arm of the LUME-Lung 1 trial[42] adenocarcinoma population
[b] Patients with RET fusion-positive NSCLC previously treated second-line or later following platinum-based chemotherapy (n=[redacted])
[c] Patients with adenocarcinoma treated second-line following prior chemotherapy, docetaxel (n=336) and nintedanib+docetaxel (n=320)
[d] Data reported in the CSR[3] only for patients with NSCLC treated any-line (n=[redacted]) of which the IAS (n=[redacted]) is a subset; hence data are reported as n/N of the patients with NSCLC treated any-line
[e] Reported as a serious AE in TA347[31]
[f] Reported as an AE of special interest in TA347[31]
ALT=alanine aminotransferase; AST=aspartate aminotransferase; WBC=white blood count
Source: CS, Table 33 and Table 47, LIBRETTO-001 CSR,[3] Table 14.3.1.4; data reported in TA347[31]

8.6 Appendix 6: EAG revisions to the company clarification model

This appendix contains details of the EAG revisions to the company model.

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td>Set up</td><td><u>In sheet ‘Results’</u>

Paste the following table into cells T35:V40
<table>
<tr><th>Name</th><th></th><th>Switch</th><th>Description</th></tr>
<tr><td>EAGcorr 1_</td><td></td><td>0</td><td>Correction: PSA utility values</td></tr>
<tr><td>EAGcorr 2_</td><td></td><td>0</td><td>Correction: PSA diagnostic testing costs</td></tr>
<tr><td>EAGcorr 3_</td><td></td><td>0</td><td>Correction: stop nintedanib treatment after 18 weeks</td></tr>
<tr><td>EAG1_</td><td></td><td>0</td><td>Use spline knot 1 PFS</td></tr>
<tr><td>EAG2_</td><td></td><td>0</td><td>Use CSR Table 14.1.1.2.1 starting dose proportions</td></tr>
<tr><td>EAG3_</td><td></td><td>0</td><td>Stop treatment at 10 years</td></tr>
</table>
Use names in ‘Name’ column to name the cells in the ‘Switch’ column</td></tr>
<tr><td>Correction: PSA utility values</td><td><u>In sheet: ‘Variables – 2LNSCLC’</u>

Set formula in cell V708
= IF(ISERROR(BETAINV(H708,J708,K708)),F708, BETAINV(H708,J708,K708))

Set formula in cell L708
= IFS(EAGcorr1_=0, V708,
AND(EAGcorr1_=1, V708<=L698), V708,
AND(EAGcorr1_=1, V708>L698), L698)</td></tr>
<tr><td>Correction: PSA diagnostic testing costs</td><td><u>In sheet: 2L NSCLC PSA Store’</u>

Set formula in cell C10
= Result_Store!H38 + IF(EAGcorr2_=1,Result_Store!H39,0)</td></tr>
<tr><td>Correction: stop nintedanib treatment after 18 weeks</td><td><u>In sheet: ‘PSM’</u>

Set value in cell BW39 = 18

Set formula in cell BY39 = IF(EAGcorr3_=0,BX38,0)

Set formula in cell Z37
= IF(MOD(C37-1,$N$8)=0,1,0)*if(and(EAGcorr3_=1,Comp_Index_Ind_1=6,PSM!B37>=18),0,1)

Copy cell Z37 down to Z38:Z1339</td></tr>
</table>

EAG revisions	Implementation instructions
Use spline knot 1 PFS	**In sheet: 'Survival – 2L NSCLC'** Set Drop Down 4 (Selpercatinib) Format Control Cell Link = Mechanics!$D$555 Set Drop Down 6 (Estimated control arm) Format Control Cell Link = Mechanics!$D$575 Set Drop Down 7 (Other comparators) Format Control Cell Link = Mechanics!$D$595 **In sheet: Mechanics'** Set formula in cell D554 = IF(EAG1_=0,D555,8) Set formula in cell D574 = IF(EAG1_=0,D575,8) Set formula in cell D594 = IF(EAG1_=0,D595,5)
Adjust selpercatinib starting dose (using CSR Table 14.1.1.2.1 starting dose proportions)	**From file: 'ID6393 Selpercatinib NSCLC_EAG starting dose.xlsx'** Copy cell formulas A1:O19 **In sheet: 'Country-Specific Data 2L NSCLC'** Paste copied formulas into cells AI96:AW114 Set formula in cell AU83 = IF(EAG2_=0,(AL83*SUMPRODUCT($Q83:$Q84,AL84:AL85))+ (AM83*SUMPRODUCT($Q83:$Q84,AM84:AM85)),AK104) Set formula in cell AU85 =IF(EAG2_=0,(BH86*SUMPRODUCT(AL84:AL85,Q83:Q84))+ (BH87*SUMPRODUCT(Q83:Q84,AM84:AM85)),AK114)
Treatment discontinuation scenario (stop treatment with selpercatinib at 10 years)	**In sheet: 'PSM'** Set formula in cell H37 = MIN(Y37,IF(Running_Ind=1,Setup_2LNSCLC!S27, IF(Running_Ind=2,Setup_1LNSCLC!S28,"error")))*IF(AND(EAG3_= 1,E36>10),0,1) Copy cell H37 down to H38:H1339

Single Technology Appraisal

Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (MA review of TA760) [ID6293]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 1 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted] in pink.

Issue 1 Feasibility of matching RET fusion-positive status and line of treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11, Section 1.4 of the EAG report states: "The company was not able to match for RET fusion-positive status or line of treatment."	Please amend the statement as follows: "The company was not able to match for RET fusion-positive status or line of treatment **because all LIBRETTO-001 trial patients had RET fusion-positive NSCLC and all REVEL trial patients had only received one previous line of treatment."**	This section of the EAG report is not currently clear that this is an inherent limitation of the available data – there was no possible method of adjusting RET fusion-positive status and line of treatment as part of the PSM process. Furthermore, as highlighted in Section 2.3 of the EAG report, there is currently no evidence to suggest that RET fusion status is a prognostic factor for patients with NSCLC. Therefore, matching for RET fusion status is expected to have a negligible impact on results. It is important that this is reflected in the EAG's summary of Key Issue 2, as has been done in Section 3.7 of its report.	The EAG agrees that the company's suggested text should have been included in Section 1.4 of the EAG report. Text amended in the updated EAG report.

Issue 2 Additional information relating to methods used in the MAIC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 of the EAG report states: "Further information regarding the methods employed to generate	Please could these statements be amended to clarify that the full methodological details associated with the MAIC were not provided	The requested methodological details associated with the MAICs, including the variables used for matching, the	Thank you for providing the additional information. The following sections have

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the unanchored MAICs (e.g., as a minimum, the prognostic factors and/or treatment effect modifiers used for matching and adjusting). Further, information regarding the success of matching and adjusting (e.g., as a minimum, comparison of baseline characteristics and reporting of effective sample size for the unanchored MAIC analyses)." Page 55 of the EAG report states: "The company did not present information about the prognostic factors and/or effect modifiers that were matched and adjusted, or how well baseline patient characteristics were balanced after this process. Nor did the company provide information about the effective sample size for each unanchored MAIC following this process." Page 59 of the EAG report states: "The company provided limited information about the methods	at the time of clarification, but were later provided by the Company.	comparison of baseline characteristics and the effective sample size have been provided in Appendix A to this response.	been amended in the updated EAG report: • Section 1.4 (Issue 4) • Section 3.6.3: study and patient characteristics • Section 3.7.3: strengths • Section 3.7.3: weaknesses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
used to carry out the unanchored MAICs, specifically: • It is not reported which prognostic factors and/or treatment effect modifiers were adjusted for in the unanchored MAICs • It is unclear whether LUME-Lung 1 trial[42] and LIBRETTO-001 trial baseline patient characteristics were well balanced across the treatment arms after matching and adjusting or whether there was any residual bias • The effective sample sizes for the treatment arms were not provided”			

Issue 3 Adjustments within PSM framework

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, Section 3.6.1 of the EAG report states: "However, the company did not adjust for differences in their estimation of treatment effects for selpercatinib versus (pseudo-control) docetaxel."	Please amend this sentence as follows: "However, the Company did not perform any further adjustments to account for any differences in patient characteristics that remained following matching."	The EAG's current wording implies that no attempts were made to adjust for differences in patient characteristics between trials, which was not the case given the propensity score matching (PSM) process undertaken by the company.	The EAG agrees that the company's suggested text is more accurate. Text amended in the updated EAG report.
Page 55, Section 3.6.3 of the EAG report states: "• the PSM approach did not result in sufficiently balanced population characteristics (selpercatinib versus (pseudo-control) docetaxel)"	Please amend this point as follows: "• **the EAG considers that** the PSM approach did not result in sufficiently balanced population characteristics (selpercatinib versus (pseudo-control) docetaxel)"	This statement represents an interpretation as to the appropriate level of matching undertaken in the company's PSM approach.	The EAG agrees that the company's suggested text is more accurate. Text amended in the updated EAG report.

Issue 4 Length of follow-up as a limitation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57, Section 3.7.1 of the EAG report states, under the "limitations" heading: "Length of study follow-up can affect results: REVEL trial[46] median OS follow-up is much shorter than LIBRETTO-001 trial median OS follow-up (8.8 months versus 44.55 months, respectively)"	This sentence should be removed from the "limitations" heading of this section.	There is no clear rationale why the difference in follow-up between the REVEL and LIBRETTO-001 trials represents a limitation. Selpercatinib is associated with substantial improvements in OS when compared to docetaxel, and therefore, it is as expected that a much longer length of OS and OS follow-up would be observed in LIBRETTO-001, compared with REVEL. If this statement is retained, additional context should be provided to detail how this represents a limitation, and to clarify that this represents a limitation of the REVEL trial, rather than the LIBRETTO-001 trial.	The EAG agrees this is a limitation of the REVEL trial. Additional context has been added to the limitations section (Section 3.7.1) of the EAG report.

Issue 5 Source of utility data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19, Page 64, Section 4.4.1 of the EAG report states:	This response should be changed to:	The NICE reference case states that the source of preference data for valuation of changes in HRQoL should be reported	To make the EAG's comment clearer, the text in the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"No. Utility values from NICE TA484[65] were used"	"**Yes**. Utility values from NICE TA484[65] were used, **which were derived from patients in the CheckMate study"**	directly by patients and/or carers, however does not specify a source (e.g. the pivotal trial for the intervention of interest). As the source of utility used in the model, TA484, was itself informed by direct EQ-5D data reported by patients with NSCLC in the CheckMate study, the company considers that NICE's reference case criterion is satisfied in this case.	report, Table 19, has been revised.

Issue 6 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, Section 2.5.5 of the EAG report states: At data cut-off, [redacted] patients were identified as no longer being on treatment. Reasons for stopping treatment were [redacted]	Please amend the bullet points as follows: At data cut-off, [redacted] patients were identified as no longer being on treatment. Reasons for stopping treatment were: [redacted]	The wording should be amended to align with the wording used in the source data from the "Systemic Anti-Cancer Therapy Dataset (SACT) Data Review. 2024" Page 23, Table 10.	The EAG agrees that the company's suggested text is more accurate. Text amended in the updated EAG report.

Issue 7 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24, Section 2.6, Table 2 of the EAG report presents the key-characteristics of the LIBRETTO-001 trial. Under the second bullet point, column 4, row 2, the patient number of the overall safety analysis set is annotated with a superscript b, for which there is no corresponding figure footnote. **Study design** / **Start date** / **Intervention** / **Population(s) for which evidence is presented in this appraisal**	Please could the EAG insert the intended figure footnote or remove the annotation.	Missing figure footnote.	Thank you. Asterix added.

Description of problem				Description of proposed amendment	Justification for amendment	EAG response
On-going, multi-centre, open-label, phase I/II single arm basket trial	May 2017	Selpercatinib (n=[redacted])	• Integrated Analysis Set: patients with previously treated, advanced RET fusion-positive NSCLC (n=[redacted]) • Overall Safety Analysis Set: all patients regardless of tumour type or treatment history (n=[redacted]			

Issue 8 Typographic error

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Page 40, Section 3.2.3, Table 8 of the EAG report states:
<table>
<tr><th>Prior treatment</th><th>16 December 2019 data-cut (n=184)</th><th>13 January 2023 data-cut (n=[redacted])</th></tr>
<tr><td>Prior cancer-related surgery, n (%)</td><td></td><td></td></tr>
<tr><td>Yes</td><td>84 (45.7)</td><td>[redacted]</td></tr>
<tr><td>No</td><td>100 (54.4)</td><td>[redacted]</td></tr>
</table>
</td>
<td>Please amend the table value of the prior cancer related surgery number in the 16th December 2019 data-cut off from 100 (54.4) to 100 (54.3) as per Table 12 of the selpercatinib EPAR.

RETSEVMO - INN: selpercatinib (europa.eu)</td>
<td>Data presented should correspond to the source.</td>
<td>Thank you. Text updated to match the correct value reported in the EPAR.</td>
</tr>
</table>

Issue 9 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 85, Section 6.5 of the EAG report states: "The EAG highlights that the [68] does not state that there is flexibility around the shortfall	Please amend the sentence as follows: "The EAG highlights that the **NICE reference case**[68] does not state that there is flexibility around the shortfall ranges that determine QALY weights."	Typographical error.	Thank you. Text updated as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ranges that determine QALY weights.”			

Issue 10 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 85, Section 6.5 of the EAG report states: “The EAG has corrected the company base case and generated cost effectiveness results by making the following revisions presented in Table 34.	Please remove the line space between “in” and “Table 34”.	Typographical error.	Thank you. Line space has been deleted.

Issue 11 Data reporting error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51, section 3.6.2 of the EAG report states: As described in Section 3.2.1, the company’s SLR identified 155 studies of second- or later-line NSCLC treatments, of	This statement should be amended to: As described in Section 3.2.1, the company’s SLR identified 155 studies of second- or later-line NSCLC treatments, of these, **30** studies could be connected in at least one network of evidence to	The EAG report incorrectly describes the number of studies included in the NMA networks – the correct values are presented in Section	The CS, Appendix D.2.2, Table 17 lists 30 RCTs included in the NMAs. However, the table does not include the LIBRETTO-001. The numbers quoted in the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
these, 31 studies could be connected in at least one network of evidence to generate NMAs. The number of studies included in the networks for each outcome ranged from 18 to 27 (ORR, n=18; PFS, n=27; OS, n=26).	generate NMAs. The number of studies included in the networks for each outcome ranged from 18 to **26** (ORR, n=18; PFS, n=**26**; OS, n=**25**).	B.2.9.2 and Table 17 in Appendix D.2.2 of the CS.	original EAG report also include the LIBRETTO-001 trial (ORR, n=18; PFS, n=27; OS, n=26). Numbers in the text of the updated EAG report have been amended to exclude the LIBRETTO-001 trial.

Issue 12 Data reporting error

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Page 54, Section 3.6.2, Table 14 of the EAG report states:
<table>
<tr><th rowspan="2">Comparator</th><th colspan="3">Treatment effect**</th></tr>
<tr><th>ORR, pairwise median OR (95% CrI)</th><th>PFS, pairwise median HR (95% CrI)</th><th>OS, pairwise median HR (95% CrI)</th></tr>
<tr><td>Docetaxel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Nintedanib+ docetaxel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Incorrectly reported values.

The ORR for selpercatinib when compared to docetaxel and docetaxel + nintedanib should be [redacted] ([redacted] - [redacted]) and [redacted] ([redacted] - [redacted]) respectively as sourced from Page 64 of document B in the NICE company evidence submission (ID6293).

Likewise, the stated value of the hazard ratio of [redacted] ([redacted] to [redacted]) should be amended to [redacted] ([redacted] to [redacted]) in the pairwise comparison of median OS between selpercatinib and nintedanib+docetaxel.</td>
<td>The pairwise ORs and HRs for selpercatinib versus docetaxel and docetaxel + nintedanib are presented on Page 64 of the Company submission Document B.</td>
<td>Thank you. The numbers have been updated in the EAG report as suggested.</td>
</tr>
</table>

Issue 13 Data reporting error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 68, Section 4.4.6 of the EAG report states: "LIBRETTO-001 trial[3] median PFS=[redacted] months;"	Please amend the sentence as follows: "LIBRETTO-001 trial[3] median PFS=[redacted] months;"	The median PFS for selpercatinib in the LIBRETTO-001 trial is incorrectly reported and should be updated in line with Table 16, Page 56 of the Company Submission Document B.	Thank you. The number has been updated in the EAG report as suggested.

Issue 14 Data reporting error

Description of problem				Description of proposed amendment	Justification for amendment	EAG response
Page 113, section 8.5.2, table 52 Adverse events, Any drug-related AE of the EAG report:				Please amend the number of "any drug-related AE" from [redacted] to [redacted] which is consistent with the data provided in the analysis of the IAS patient sample in the LIBRETTO-001 trial.	The number of patients experiencing any-grade adverse events related to selpercatinib is incorrectly reported, and should be updated in line with Table 31, Page 77 of the Company Submission Document B.	Thank you. The numbers have been updated in the EAG report as suggested.

Type of AE	LIBRETTO-001 IAS population[a]	LUME-Lung 1 adenocarcinoma population[b]	
	Selpercatinib n (%)	Docetaxel n (%)	Docetaxel+ nintedanib n (%)
Any	[redacted]	314 (94.3)	308 (96.3)
Any drug-related AE	[redacted]	241 (72.4)	260 (81.3)
Grade ≥3 AE	[redacted]	228 (68.5)	243 (75.9)
AE leading to	[redacted]	59 (17.7)	67 (20.9)

Description of problem				Description of proposed amendment	Justification for amendment	EAG response
treatment discontinuation						
SAE	[redacted]	107 (32.1)	111 (34.7)			
Fatal AE	[redacted]	32 (9.6)	56 (17.5)			
Fatal AE related to treatment	[redacted]	1 (0.3)	6 (1.9)			

Issue 15 Data reporting error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 72, Section 4.4.9 of the EAG report states: "All the cost estimates were derived using information from previous NICE Technology Appraisals (TA484,[65] TA516,[75] TA520,[74] TA621 [76])"	Please amend this sentence as follows: "All the cost estimates were derived using information from previous NICE Technology Appraisals (**TA428**[ref], TA484,[65] TA516,[75] TA520,[74] TA621 [76])"	The list of past NICE appraisals used to derive costs excludes TA428, which was also used.	Thank you. The TA number has been updated in the EAG report as suggested.

Issue 16 Data reporting error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, Section 6.3.1 of the EAG report states:	Please amend this sentence as follows: "The EAG has retained the company approach to generating nintedanib+docetaxel	The Company used the spline-knot 3 as a reference curve when modelling nintedanib + docetaxel PFS, as detailed in	The EAG agrees that the original text could be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG has retained the company approach to generating nintedanib+docetaxel PFS estimates by applying the company PFS NMA HR to the spline knot 1 (pseudo-control) docetaxel curve."	PFS estimates by applying the company PFS NMA HR to the spline knot **3** (pseudo-control) docetaxel curve."	Section B.3.3.6 of the Company Submission Document B.	misinterpreted. For clarity, text has been added.

Issue 17 Data reporting error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83, Section 6.4 of the EAG report states: "The company's generalised gamma distribution fitted to LIBRETTO-001 trial[3] data resulted in [redacted]% of patients receiving treatment for more than 10 years and [redacted]% of patients receiving treatment for up to 25 years."	Please amend this sentence as follows: "The company's generalised gamma distribution fitted to LIBRETTO-001 trial[3] data resulted in [redacted]% of patients receiving treatment for more than 10 years and [redacted]% of patients receiving treatment for up to 25 years."	The TTD outcomes associated with the generalised gamma distribution are incorrect, and should be updated to align with Table 46 in the CS Document B.	Thank you. The numbers have been updated in the EAG report as suggested.

Issue 18 Request for clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36 of the EAG report states Overall, 14 studies included patients with RET-altered tumours, suggesting that the company SLR included four RCTs of patients with RET-altered tumours; these four RCTs were not included in the company NMAs.	Please could this statements be amended to clarify that the four RCTs including patients with RET-altered tumours were not included in the Company NMAs **because none of the trial publications reported any results for patients with RET-altered NSCLC as RET testing was done retrospectively; the number of patients with RET alterations was small, and all four of the RCTs studied vandetanib, which is not a relevant comparator for the submission.**	As discussed on page 45 of the Company's SLR report, the SLR included four vandetanib RCTs where small number of patients with RET-altered tumours were identified retrospectively. These four RCTs were not eligible for the company NMAs as vandetanib is not an approved treatment for NSCLC by EMA and so is not a comparator of interest. Please could the include this discussion in their report to clarify why the RCTs were not included in the NMAs.	Thank you for the additional information. Text has been added to the EAG report.

Issue 19 Request for clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 30, Page 77 of the EAG Report has a column labelled "Impact on cost effectiveness results (no severity modifier)"	Please could this heading be updated to the following: "Impact on the pairwise ICER for selpercatinib versus each comparator (no severity modifier)"	It is currently unclear whether this column refers to incremental costs or the ICER between selpercatinib and each comparator – please could the EAG amend this column heading so that this is clear.	For clarity, text has been amended in the EAG report, as suggested.

Confidentiality highlighting inaccuracies

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr>
<td>Page 39, Section 3.2.3, Table 7</td>
<td>Age group and disease stage breakdown data in the 13 January 2023 data-cut of the LIBRETTO-001 trial are unpublished and therefore should be marked as confidential in the EAG report.</td>
<td>
<table>
<tr><th>Baseline characteristic</th><th>16 December 2019 data-cut (n=184)</th><th>13 January 2023 data-cut (n=[redacted])</th></tr>
<tr><td>Age, years</td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>62.0 (23 to 81)</td><td>61.0 (23 to 81)</td></tr>
<tr><td>Age group, n (%)</td><td></td><td></td></tr>
<tr><td>18-44 years</td><td>26 (14.1)</td><td>[redacted]</td></tr>
<tr><td>45-64 years</td><td>89 (48.4)</td><td>[redacted]</td></tr>
<tr><td>65-74 years</td><td>54 (29.3)</td><td>[redacted]</td></tr>
<tr><td>≥75 years</td><td>15 (8.2)</td><td>[redacted]</td></tr>
<tr><td>Disease stage at diagnosis, n (%)</td><td></td><td></td></tr>
<tr><td>I-II</td><td>4 (2.2)</td><td>[redacted]</td></tr>
<tr><td>III</td><td>10 (5.4)</td><td>[redacted]</td></tr>
<tr><td>IV</td><td>170 (92.4)</td><td>[redacted]</td></tr>
<tr><td>Time from diagnosis, months</td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>24.2 (1.5 to 164.8)</td><td>[redacted]</td></tr>
<tr><td>Primary NSCLC diagnosis, n (%)</td><td></td><td></td></tr>
<tr><td>Adenocarcinoma</td><td>Not reported</td><td>221 (89.5)</td></tr>
<tr><td>History of metastatic disease, n (%)</td><td></td><td></td></tr>
<tr><td>Yes</td><td>179 (97.3)</td><td>[redacted]</td></tr>
<tr><td>Time from diagnosis of metastatic disease,</td><td></td><td></td></tr>
</table>
</td>
<td>Apologies for these errors, the EAG experienced formatting issues with this table when finalising its original report. Correct confidential marking has now been applied as suggested.</td>
</tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		months, n (%)	
		Median (range)	19.5 (1.0 to 108.1)
		CNS metastasis at baseline by investigator, n (%)	
		Yes	60 (32.6)
Page 41, Section 3.3.1	[redacted] is not publicly announced, and should therefore be marked as confidential in the EAG report.	Unlike the 16 December 2019 data-cut, [redacted] by the 13 January 2023 data-cut.	Data have now been marked as confidential in the updated EAG report as requested.
Page 42, Section 3.3.1	[redacted]	The EAG notes the following differences between the IRC-assessed and investigator assessed results: • [redacted] were observed for patients considered to have a complete response, partial response or stable disease; however ORR was [redacted] assessed by IRC or investigator (Appendix 2, Section 8.2.1, Table 43) • the median DoR was notably [redacted] for patients classified as responding by IRC than by investigator (Appendix 2, Section 8.2.1, Table 44) • [redacted] were observed for the number of patients considered to have disease progression largely as a result of a [redacted] number of patients censored by the IRC than investigator as a result of subsequent therapy/surgery without documented progressed disease; however median	Text has now been marked as confidential in the updated EAG report as requested.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		PFS was [redacted] assessed by IRC or investigator (Appendix 2, Section 8.2.2, Table 45).	
Page 44, Section 3.4	The EAG report describes the PROs of the LIBRETTO-001 trial which are not publicly announced and therefore should be marked a confidential in the EAG report.	The company reported (CS, p61) that, "[redacted]" of previously treated advanced RET fusion-positive NSCLC patients had experienced [redacted] in quality of life across the period of treatment with selpercatinib as determined by QLQ-C30 subscales." However, the EAG notes (CS, Appendix L.1, Table 42) that, while a [redacted] proportion of patients reported an "improvement" rather than a "worsening" at most cycle visits, for most subscales, up to the final cycle (Cycle 49), this [redacted] of all patients who completed the assessment at that visit. For the cognitive functioning and diarrhoea subscales, at most cycle visits, [redacted] reported "worsening" rather than "improvement". As it is not known which patients reported an "improvement" and which patients reported a "worsening" at any given visit, it is only possible to conclude that, on occasion, [redacted]. The presented data suggest that "[redacted]" of patients at least [redacted] their HRQoL at every visit during treatment and at EOT.	As requested, this text has now been marked as confidential in the updated EAG report. However, it should be noted that none of the text in the first sentence was marked as confidential in the company submission (p61).

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 45, Section 3.5.2	The EAG report describes safety data from LIBRETTO-001 which are not publicly announced and therefore should be marked a confidential in the EAG report.	Grade 3 or 4 AEs and serious AEs (SAEs) were [redacted] but were much [redacted] linked to treatment with selpercatinib. Permanent discontinuation of selpercatinib due to TEAEs or TRAEs was relatively [redacted].	As requested, text has now been marked as confidential in the updated EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 46, Section 3.5.2	The EAG report describes safety data from LIBRETTO-001 which are not publicly announced and therefore should be marked a confidential in the EAG report.	Rates of the most common (≥15%) TEAEs were [redacted] between the OSAS and IAS populations, although fatigue, rash and abdominal pain were [redacted] in the OSAS population than in the IAS population (CS, Table 32). The most common AE in the IAS population was [redacted], which was experienced by [redacted] ([redacted], [redacted]) of patients with pre-treated RET fusion NSCLC (and [redacted] of all patients in the OSAS population: [redacted], [redacted]). The [redacted] (Table 11) were AEs of special interest (AEOSI): hypertension, alanine aminotransferase (ALT) increase, aspartate aminotransferase (AST) increase and electrocardiogram (ECG) QT prolonged (CS, Table 33). AEOSIs were identified a priori based on predictions from the RET-related literature, the preclinical toxicology programme and clinical experience with selpercatinib (CS, p79). A fifth AEOSI was hypersensitivity. While AEOSIs were [redacted], [redacted], and [redacted]. The company reported (CS, p74 and p79) that common TEAEs (including AEOSIs) were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication. Permanent discontinuation due to AEOSIs was [redacted].	As requested, text has now been marked as confidential in the updated EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 52, Section 3.5.2	The EAG report describes baseline characteristic data from the LIBRETTO-001 trial which are not publicly announced and therefore should be marked a confidential in the EAG report.	The EAG has presented key LIBRETTO-001 trial,[3] REVEL trial[46] and LUME-Lung 1 trial[42] patient baseline characteristics (Appendix 4, Section 8.4.1, Table 48). These data show that: • REVEL trial[46] and LUME-Lung 1 trial[42] baseline characteristics are broadly similar • the LIBRETTO-001 trial enrolled proportionately [redacted] than the REVEL trial[46] or the LUME Lung-1 trial;[42] these characteristics are considered more common in patients with RET fusion-positive NSCLC • the LUME-Lung 1 trial[42] included proportionately [redacted] patients who were diagnosed with Stage III NSCLC (particularly in the nintedanib+docetaxel arm) than in either the LIBRETTO-001 trial or in the REVEL trial[46]	As requested, text has now been marked as confidential in the updated EAG report.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 56, Section 3.6.2	The EAG report describes the results of the unanchored MAIC which are not publicly announced and therefore should be marked a confidential in the EAG report.	For selpercatinib versus both comparators, the results showed that unanchored MAICs generated [redacted] ORs for ORR and [redacted] HRs for PFS and OS than the NMA results. The company considered that these results showed that the NMA approach generated conservative estimates of the relative treatment effects of selpercatinib versus both comparators (company response to clarification question A1).	As requested, text has now been marked as confidential in the updated EAG report.
Pages 68, 69, Section 4.4.6	AIC and BIC rankings of OS extrapolations are confidential.	"Based on AIC and BIC scores, the loglogistic and exponential functions ranked [redacted]." "Clinical advice to the company was that the loglogistic function (AIC: rank=[redacted]; BIC: rank=[redacted]) […]" AIC: rank=[redacted]; BIC: rank=[redacted]; "(AIC: rank=[redacted]; BIC: rank=[redacted])"	As requested, text has now been marked as confidential in the updated EAG report.
Page 68, Section 4.4.6	The percentage of patients who are progression-free at 20 years is confidential.	"[redacted]% of patients being progression-free at 20 years"	This text was already marked as confidential

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td>in the EAG report.</td></tr>
<tr><td>Page 107, Section 8.4.1, Table 48

Table 1 LIBRETTO-001 trial, REVEL trial and LUME-Lung 1 trial baseline characteristics</td><td>This table refers to data from the 13 January 2023 data-cut of the LIBRETTO-001 trial, which is confidential. Therefore, patient numbers should be redacted.</td><td>
<table>
<tr><th rowspan="2">Baseline characteristic</th><th>LIBRETTO-001 trial IAS population</th><th>REVEL trial</th><th colspan="2">LUME-Lung 1 trial adenocarcinoma population</th></tr>
<tr><th>Selpercatinib (n=[redacted])</th><th>Docetaxel (n=447)[a]</th><th>Docetaxel (n=336)</th><th>Nintedanib+ docetaxel (n=322)</th></tr>
<tr><td>Age, years</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>61 (23 to 81)</td><td>61 (25 to 86)</td><td>59 (30 to 80)</td><td>60 (29 to 80)</td></tr>
<tr><td>Age group, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td><65 years</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>≥65 years</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Sex, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>140 (56.7)</td><td>170 (38.0)</td><td>128 (38.1)</td><td>119 (37.0)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Asian</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>Apologies for these errors, the EAG experienced formatting issues with this table when finalising the original report. However, only the data for the LIBRETTO-001 trial should be marked as confidential as the EAG has extracted REVEL and LUME-Lung 1 trial data from published sources.</td></tr>
</table>

(Please add further lines to the table as necessary)

Appendix A: Additional Details on the

Methodology

Five covariates were adjusted for as part of the MAICs:

- Age
- Sex
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- Smoking status
- Brain metastases

Baseline characteristics (selpercatinib versus docetaxel chemotherapy with placebo)

A summary of baseline characteristics in LIBRETTO-001 before and after weighting, compared to the population of patients receiving docetaxel chemotherapy plus placebo in LUME-1 for Table 2 (for the PFS MAIC) and Table 3 (for the OS MAIC), as well as the effective sample size for LIBRETTO-001 after weighting.

Table 2: Comparison of baseline characteristics before and after weighting in LIBRETTO-001 versus LUME-1 (PFS MAIC, selpercatinib versus docetaxel chemotherapy with placebo)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=285**
Sex	Female	140 (56.68%)	[redacted]	107 (37.5%)
Age	< 65	[redacted]	[redacted]	204 (71.6%)
Smoking history	Never smoked	165 (66.80%)	[redacted]	100 (35.1%)
ECOG performance status	0	90 (36.44%)	[redacted]	84 (29.5%)
Brain metastases	Yes	77 (31.17%)	[redacted]	20 (7.0%)

Footnotes: *Effective sample size
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; MAIC: matching adjusted indirect comparison; NSCLC: Non-small cell lung cancer; PFS: progression-free survival.

Table 3: Comparison of baseline characteristics before and after weighting in LIBRETTO-001 versus LUME-1 (OS MAIC, selpercatinib versus docetaxel chemotherapy with placebo)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=336**
Sex	Female	140 (56.68%)	[redacted]	128 (38.1%)
Age	< 65	[redacted]	[redacted]	240 (71.4%)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=336**
Smoking history	Never smoked	165 (66.80%)	[redacted]	115 (34.2%)
ECOG performance status	0	90 (36.44%)	[redacted]	99 (29.5%)
Brain metastases	Yes	77 (31.17%)	[redacted]	23 (6.8%)

Footnotes: *Effective sample size
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; MAIC: matching adjusted indirect comparison; NSCLC: Non-small cell lung cancer; OS: overall survival. .

Baseline characteristics (selpercatinib versus docetaxel chemotherapy with nintedanib)

A summary of baseline characteristics in LIBRETTO-001 before and after weighting, compared to the population of patients receiving docetaxel chemotherapy plus nintedanib in LUME-1 for Table 4 (for the PFS MAIC) and Table 5 (for the OS MAIC), as well as the effective sample size for LIBRETTO-001 after weighting.

Table 4: Comparison of baseline characteristics before and after weighting in LIBRETTO-001 versus LUME-1 (PFS MAIC, selpercatinib versus docetaxel chemotherapy with nintedanib)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=277**
Sex	Female	140 (56.68%)	[redacted]	103 (37.2%)
Age	< 65	[redacted]	[redacted]	200 (72.2%)
Smoking history	Never smoked	165 (66.80%)	[redacted]	96 (34.7%)
ECOG performance status	0	90 (36.44%)	[redacted]	82 (29.6%)
Brain metastases	Yes	77 (31.17%)	[redacted]	23 (8.3%)

Footnotes: *Effective sample size
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; MAIC: matching adjusted indirect comparison; NSCLC: Non-small cell lung cancer; PFS: progression-free survival.

Table 5: Comparison of baseline characteristics before and after weighting in LIBRETTO-001 versus LUME-1 (OS MAIC, selpercatinib versus docetaxel chemotherapy with nintedanib)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=322**
Sex	Female	140 (56.68%)	[redacted]	119 (37.0%)

		LIBRETTO-001 NSCLC		
Characteristics	**Category**	**Before weighting N=247**	**After weighting N=[redacted]**	**LUME-Lung1 N=322**
Age	< 65	[redacted]	[redacted]	232 (72.0%)
Smoking history	Never smoked	165 (66.80%)	[redacted]	115 (35.7%)
ECOG performance status	0	90 (36.44%)	[redacted]	96 (29.8%)
Brain metastases	Yes	77 (31.17%)	[redacted]	26 (8.1%)

Footnotes: *Effective sample size
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; MAIC: matching adjusted indirect comparison; NSCLC: Non-small cell lung cancer; OS: overall survival.