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

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist/review manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributing to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Bram Ramaekers, Manuela Joore, Thomas Otten, Andrea Coves Fernandez and Teebah Abu-Zarah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ACTH	Adrenocorticotropic hormone
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATEZ	Atezolizumab
BEV	Bevacizumab
BIC	Bayesian information criteria
BICR	Blinded Independent Committee Review
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
c	Continuous
CADTH	Canadian Agency for Drugs and Technologies in Health
CAMR	Camrelizumab
CARB	Carboplatin
CASP	Critical Appraisal Skills Programme
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CEMIPL	Cemiplimab
CENTRAL	Cochrane Central Register of Controlled Trials
Cf-DNA	Circulating free DNA
CI	Confidence interval
CIS	Cisplatin
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete response
CrI	Credible intervals
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
Dbar	Mean sum of residual deviances
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DURV	Durvalumab
ECG	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
EAG	Evidence Assessment Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
eMIT	electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Platform of Cancer Research Quality of Life Questionnaire

EORTC QLQ–C30	European Platform of Cancer Research Quality of Life Questionnaire core 30
EoT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
ERL	Erlotinib
EUR	Erasmus University Rotterdam
FE	Fixing errors
FV	Fixing violations
FISH	Fluorescence in-situ hybridisation
GEF	Gefitinib
GEM	Gemcitabine
HIV	Human immunodeficiency virus
HR(s)	Hazard ratio(s)
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Appraisal
i	Induction
IA	Investigator Assessment
IAS	Integrated Analysis Set
ICER(s)	Incremental cost-effectiveness ratio(s)
ICTRP	International Clinical Trials Registry Platform
ID	Identification
iNHB	incremental net health benefit
iNMB	incremental net monetary benefit
IPD	Individual patient data
IPI	Ipilimumab
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Limited
LPS	Lansky Performance Score
LTFU	Lost to follow-up
LY(s)	Life year(s)
M	Maintenance
MJ	Matters of judgement
MSI	Microsatellite instability
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
N	Number of patients
n	Number of patients in specific category
N/A	Not applicable
Nab-PAC	Nab-paclitaxel
NCI CTCAE	National Cancer Institute common terminology for AEs
NCT	National Clinical Trial
NE	Not estimable
NG122	NICE guideline 122
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIVO	Nivolumab
NL	Netherlands
NMA	Network meta-analysis

NMB	Net monetary benefit
No	Number
NR	Not reported
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
OSAS	Overall Safety Analysis Set
PAC	Paclitaxel
PAS	Primary Analysis Set
PAS	Patient Access Scheme
PCB	Placebo
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1 receptor
PD-L1	Programmed death receptor ligand 1
PEM	Pemetrexed
PEMBRO	Pembrolizumab
PF	Progression-free
PFLY(s)	Progression-free life year(s)
PFS	Progression-free survival
PK	Pharmacokinetic
PLAT	Platinum chemotherapy
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSM	Propensity score matching
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PSW	Propensity score weighting
QALY(s)	Quality-adjusted life year(s)
QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
OS	Overall survival
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended Phase II dose
RAM	Ramucirumab
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT(s)	Randomised controlled trial(s)
RDI	Relative dose intensity
RE	Random-effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
RMST	restricted mean survival time
RP2D	Recommended phase 2 dose
RT	Radiation therapy

RWE	Real world evidence
SAS	Safety Analysis Set
SAS	Supplemental Analysis Set
SAS1	Supplemental Analysis Set 1
SAS2	Supplemental Analysis Set 2
SAS3	Supplemental Analysis Set 3
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SD	Stable disease
SEL	Selpercatinib
SFU	Safety follow-up
SINT	Sintilimab
SIREN	Selpercatinib in RET fusion-positive non-small-cell lung cancer
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STM	State transition model
TA(s)	Technology Appraisal(s)
TEAE(s)	Treatment emergent adverse event(s)
TISL	Tislelizumab
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC+	University Medical Center+
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues are related to the cost-effectiveness while a summary is in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost-effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Population: uncertainty as to whether includes squamous histology for which no evidence has been provided.	2.1
2	Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates.	2.2, 3 to 6
3	Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.	3.2.4
4	Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated.	3
5	Applicability: there is the possibility of differences between trial and UK target population in race and CNS metastases (due to limited information). Combined with evidence of the possibility that race and CNS metastases are effect modifiers, this implies that results from the trial may not be applicable to the UK target population.	3.2.5.6
6	Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.	3.2.8
7	ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators.	3.4
8	ITC: methods of adjustment for confounding might have biased comparison with all comparators.	3.4
9	NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy.	3.4.2
10	No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms.	3.4.2.4
11	Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period.	4.2.2 and 5.2

ID1457	Summary of issue	Report Sections
12	Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model.	4.2.6
13	The company's choice of survival curves for the modelling of treatment effectiveness was not transparent.	4.2.6
14	Waning of the selpercatinib treatment effect was not explored.	4.2.6
15	Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib.	4.2.6 and 5.1
16	Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states.	4.2.8
17	The plausibility of the company's choices for the modelling of subsequent treatments.	4.2.9

ICERs = incremental cost-effectiveness ratios; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PSM = propensity score matching; SAS1 = supplemental analysis set 1; STM = state transition model; UK = United Kingdom

1.2 Overview of key model outcomes

National Institute for Health and Care Excellence technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival (PFS) for selpercatinib (QALYs in the progression-free (PF) health state increased by [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and increased overall survival (OS) for selpercatinib (survival (undiscounted) increased by [redacted] and [redacted] years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). This resulted in post-progression benefits of [redacted] and [redacted] QALYs compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (estimates retrieved from company submission (CS), Appendix J).
- Treatment benefit (in terms of OS and PFS) are maintained for the whole duration of the time horizon i.e., no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and higher disease management costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). These costs are partly offset by lower subsequent treatment costs (cost savings of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively; estimates retrieved from CS, Appendix J).

The parameters that have the greatest effect on the ICER (based on the company's deterministic sensitivity analyses) were:

- Discount rate for costs
- Discount rate for outcomes
- Drug administration costs
- Subsequent active systemic anticancer therapy costs
- Drug related monitoring costs
- Adverse event costs

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the ICER were related to:

- Estimation of time to treatment discontinuation (TTD)
- Estimation of PFS
- Estimation of OS
- Subsequent therapy distribution
- Assuming alternative utility values (from TA654)

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue 1: Population: uncertainty as to whether includes squamous histology for which no evidence has been provided

Report Section	**2.1**
Description of issue and why the EAG has identified it as important	No evidence was provided for the squamous population, but the company want the population for which NICE considers selpercatinib to include it. The FAC has also revealed that a license extension has been granted by the MHRA to include patients who have been previously treated, except with a RET inhibitor.[1] The EAG notes that the evidence that has been submitted was consistent with the scope in terms of patients being treatment naïve and not with the license extension.
What alternative approach has the EAG suggested?	The EAG would argue that the relevant population should only be non-squamous histology.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence in the squamous population if it is to be included in a recommendation by NICE. Further evidence would need to be submitted if the scope was to be broadened to include patients who are not untreated.
EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2: Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates

Report Section	**2.2, 3 to 6**
Description of issue and why the EAG has identified it as important	Some comparators in the scope and which are recommended in the latest NICE guideline, NG122, are not included in the decision problem and thus the clinical effectiveness and cost-effectiveness analyses. The limited array of comparators in the decision problem (two) may have influenced interpretations. Had other comparators been present, as requested by the NICE scope,

Report Section	2.2, 3 to 6
	selpercatinib may not have emerged as the most effective and cost-effective treatment.
What alternative approach has the EAG suggested?	Include all comparators in the scope.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide evidence that the omitted comparators are not being used in NHS clinical practice or evidence of selpercatinib's clinical effectiveness and cost-effectiveness versus those comparators.
EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.4: Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice

Report Section	3.1.2, 3.3, 3.4, and 4
Description of issue and why the EAG has identified it as important	There are discrepancies between the subsequent therapies used in the LIBRETTO-001 trial and clinical expert opinion as to UK clinical practice. In particular, percentage use in LIBRETTO-001 (numbers unclear) versus. assumed in clinical practice are: • pemetrexed plus platinum chemotherapy: very low in (precise number difficult to ascertain) versus. 70% • best supportive care: apparently none versus. 20% • pembrolizumab plus pemetrexed and platinum chemotherapy: [redacted] might have received pembrolizumab in some combination versus. 5%. This could lead to trial results that are not applicable to the target population.
What alternative approach has the EAG suggested?	Clarity as to the distribution of subsequent therapies in LIBRETTO-001. Costing in the economic model in line with the trial.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated either due to bias in effectiveness or cost.
What additional evidence or analyses might help to resolve this key issue?	Clarity as to the distribution of subsequent therapies in LIBRETTO-001. Costing in the economic model in line with the trial.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

Table 1.5: Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated

Report Section	3.1.2, 3.3, and 3.4
Description of issue and why the EAG has identified it as important	The submission relies on a single arm study of selpercatinib, LIBRETTO-001 compared via an ITC with a pemetrexed plus platinum chemotherapy single arm from another trial, KEYNOTE-189, and pembrolizumab with pemetrexed plus platinum chemotherapy via an NMA including KEYNOTE-189,

Report Section	3.1.2, 3.3, and 3.4
	-189 Japan and -021, all in a largely non-*RET* fusion-positive population. However, there is evidence, albeit of low quality, that the effectiveness of pemetrexed might be considerably higher in the RET fusion-positive population. Also, results for an RCT, LIBRETTO-431 versus both comparators in the decision problem in the RET fusion-positive population might be available during 2023.
What alternative approach has the EAG suggested?	Attempt to obtain comparator evidence in the RET fusion-positive population for the ITC and NMA.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Attempt to obtain comparator evidence in the RET fusion-positive population for the ITC and NMA. Obtaining the RCT data is by far the best option.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; NMA = network meta-analysis; RCT = randomised controlled trial; RET = rearranged during transfection	

Table 1.6: Key issue 5: Applicability based on population characteristics: there is no information on the characteristics of UK target population

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The data showed similarities between a UK survey and the SAS1 trial dataset in age, but differences in sex, ECOG score and molecular assay type. Although the data on ethnicity were similar between the UK survey and the SAS1 trial dataset, these data did not differentiate between important ethnic groups in the UK. No data were provided for UK patients on history of metastatic disease. Meanwhile, the sub-group analyses demonstrated that any metastatic disease, CNS metastases, and age may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier. Whilst it is true that none of the results of the subgroup analysis were found to be statistically significant, a lack of statistical significance is not particularly informative in analyses that were not sufficiently powered, and the EAG believes that the point estimate differences are of sufficient magnitude to imply the possibility of type II errors. Therefore, the possibility that any metastatic disease, CNS metastases and race may differ between trial and target population (in the absence of adequate information) and the evidence that CNS metastases and race are possible effect modifiers make it possible that the effects in the trial may not be applicable to those that might be observed in the target population.
What alternative approach has the EAG suggested?	Provide characteristics of the UK target population.

Report Section	3.1.2, 3.3, 3.4
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide characteristics of the UK target population.
CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EAG = Evidence Assessment Group; UK = United Kingdom	

Table 1.7: Key issue 6: Adverse events: there are no specific adverse event data for the eligible participants relevant to the decision problem

Report Section	3.2.8
Description of issue and why the EAG has identified it as important	There are no specific adverse event data for the eligible participants relevant to the decision problem: the treatment naïve subset (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321. This is a potential problem as it is it is not possible to exclude a greater concentration of adverse events in this subgroup than are observed overall.
What alternative approach has the EAG suggested?	Provide adverse events data specific to the eligible subsets.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide adverse events data specific to the eligible subsets.
EAG = Evidence Assessment Group; SAS = safety analysis set	

Table 1.8: Key issue 7: ITC: choice of trial data might have biased comparison with all comparators

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The company stated that the choice of trial (KEYNOTE-189) was determined by access to individual patient data, which permitted the best method of conducting the ITC. The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm is stated as being due to relevant IPD not being available from any other sources, which the EAG consider to be not a convincing rationale. It is likely that had other sources of pemetrexed plus platinum chemotherapy data been used, then very different overall NMA results might have been yielded.
What alternative approach has the EAG suggested?	Consider another source of individual patient data such as KEYNOTE-021.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Consider another source of individual patient data such as KEYNOTE-021.

Report Section	3.1.2, 3.3, 3.4
EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NMA = network meta-analysis; RCT = randomised controlled trial	

Table 1.9: Key issue 8: ITC: methods of adjustment for confounding might have biased comparison with all comparators

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The methodology used for matching of the pseudo-comparator arm to the selpercatinib arm may not have been optimal. Of the methods explored, all of which had comparable baseline characteristic balance deficits, it appears that the default PSM method led to the most conservative results, which initially supports the presentation of results based upon this method. However, because the array of methods explored by the company were limited, it is possible that unexplored methods leading to a better degree of balance (such as addition of multivariate regression on the matched sample) might have yielded results that were less favourable to selpercatinib than those observed by the default PSM approach. It is also possible, given lack of rationale for choice of covariates, that important ones such as RET fusion status and brain metastases have been omitted.
What alternative approach has the EAG suggested?	Addition of multivariate regression on the matched sample. Consideration of other covariates and selecting only RET fusion-positive comparator patients.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Addition of multivariate regression on the matched sample. Consideration of other covariates and selecting only RET fusion-positive comparator patients.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; PSM = propensity score matching; RET = rearranged during transfection	

Table 1.10: Key issue 9: NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	Possible differences between studies in ethnicity/clinical practice (KEYNOTE-189 Japan was comprised only of Japanese patients) suggest possible clinical heterogeneity across the three pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy trials. This is supported by large differences in point estimates across the three trials in both OS and PFS outcomes. Statistical heterogeneity for either outcome was not detected on I^2 testing. However, this may be a type II error, given that the study was not powered for such analyses, and in view of the clinical heterogeneity and the large point estimate differences. Another potential source of heterogeneity is RET fusion status. Although this does not seem to be available for any of the trials in the NMA, if it were for KEYNOTE-189 then the other two

Report Section	3.1.2, 3.3, 3.4
	trials could be excluded for the comparison with pembrolizumab plus pemetrexed plus platinum chemotherapy.
What alternative approach has the EAG suggested?	Re-analysis after removal of studies e.g., KEYNOTE-189 Japan.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Re-analysis after removal of studies e.g., KEYNOTE-189 Japan.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection	

Table 1.11: Key issue 10: No NMA or comparative analysis was carried out for adverse events

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	No NMA or any kind of comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms.
What alternative approach has the EAG suggested?	A comparison between selpercatinib and all comparators, including an NMA, should be added for adverse events.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A comparison between selpercatinib and all comparators, including an NMA, should be added for adverse events.
EAG = Evidence Assessment Group; NMA = network meta-analysis	

1.5 The cost-effectiveness evidence : summary of the EAG's key issues

A full summary of the cost-effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost-effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential Patient Access Schemes (PAS) in a confidential appendix. The key issues in the cost-effectiveness evidence are discussed in the issue Tables below.

Table 1.12: Issue 11: Model structure

Report Section	4.2.2 and 5.2
Description of issue and why the EAG has identified it as important	NICE DSU TSD 19 recommends the use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period.
What alternative approach has the EAG suggested?	Compare the results of the partitioned survival model to the outcomes of a state transition model.

Report Section	4.2.2 and 5.2
What is the expected effect on the cost-effectiveness estimates?	According to the EAG there is considerable uncertainty related to the extrapolation of the PFS and OS endpoints in the selpercatinib arm. This uncertainty has a potentially substantial impact on the ICER as the large majority of gains in the economic model are accumulated beyond the observed data period.
What additional evidence or analyses might help to resolve this key issue?	Use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NICE DSU TSD 19 = National Institute for Health and Clinical Excellence Decision Support Unit Technical Support Document 19; OS = overall survival; PFS = progression-free survival	

Table 1.13: Key issue 12: Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The data obtained from the LIBRETTO-001 trial for OS and PFS are immature, adding substantial uncertainty to the extrapolated survival data in the economic model.
What alternative approach has the EAG suggested?	To reflect the uncertainty due to data immaturity, and resulting ambiguity in choice of survival curves, the EAG conducted scenario analyses to find the range of results given plausible parametric survival curves.
What is the expected effect on the cost-effectiveness estimates?	The scenario analyses resulted in iNMB ranges of around £28.000 for both comparators: pembrolizumab combination therapy: £39,808 to £67,101, pemetrexed plus platinum chemotherapy: -£36,197 to -£8,192
What additional evidence or analyses might help to resolve this key issue?	Long-term PFS and OS data to reduce the uncertainty around the cost-effectiveness results.
EAG = Evidence Assessment Group; iNMB = incremental net monetary benefit; OS = overall survival; PFS = progression-free survival	

Table 1.14: Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company's choice of survival curves for the modelling of treatment effectiveness was not transparent.
What alternative approach has the EAG suggested?	The EAG would like to receive more detail and justification concerning the choice of parametric survival curves.
What is the expected effect on the cost-effectiveness estimates?	Unknown.

What additional evidence or analyses might help to resolve this key issue?	The EAG would like to receive more detail concerning the choice of parametric survival curves. Specifically, the EAG would like to see more information about a) the choice of considering complex survival curves, b) the plots that were not provided in the clarification response c) the choice between survival curves in detail and d) the mismatch between reported PFS and OS values in the CS and values used in the economic model.
CS = company submission; EAG = Evidence Assessment Group; OS = overall survival; PFS = progression-free survival	

Table 1.15: Key issue 14: Waning of the selpercatinib treatment effect was not explored

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	The company did not explore waning of the selpercatinib treatment effect in the submission.
What alternative approach has the EAG suggested?	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time. An updated model and scenario analyses to explore the impact of treatment waning into the model.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time. An updated model and scenario analyses to explore the impact of treatment waning (kicking in at different time points) into the model.
EAG = Evidence Assessment Group; OS = overall survival; PFS = progression-free survival	

Table 1.16: Key issue 15: Company's estimated progression-free life years for pemetrexed plus platinum chemotherapy

Report Section	**4.2.6 and 5.1**
Description of issue and why the EAG has identified it as important	The observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated.
What alternative approach has the EAG suggested?	Alternative approaches to estimate PFS for pemetrexed plus platinum chemotherapy where the modelled PFS > observed PFS for pemetrexed plus platinum chemotherapy.
What is the expected effect on the cost-effectiveness estimates?	Based on the CS scenario analyses (as summarised in Section 5.2 of this report), PFS was amongst the modelling assumptions that have the greatest effect on the ICER.
What additional evidence or analyses	Long-term PFS data.

Report Section	4.2.6 and 5.1
might help to resolve this key issue?	
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival	

Table 1.17: Key issue 16: Health-related quality of life

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The utility values from the company's base-case were higher than the ones used in other TAs, only slightly lower than the age and gender matched UK general population and had a small decrement between PF and PD states.
What alternative approach has the EAG suggested?	The EAG requested scenario analyses exploring utility values from other relevant TAs. The EAG implemented the PD utility from TA654 in its base-case.
What is the expected effect on the cost-effectiveness estimates?	All provided scenario analyses including utility values from other TAs resulted in higher ICER than the company's base case. Implementing the PD utility from TA654 increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	N/A.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; PF = progression-free; PD = progressed disease; TA = Technology Appraisal; UK = United Kingdom	

Table 1.18: Key issue 17: Resources and costs

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The plausibility of the company's choices for the modelling of subsequent treatments.
What alternative approach has the EAG suggested?	Informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Informing subsequent treatments for the comparators based on NG122 and expert oncologist inputs.
What is the expected effect on the cost-effectiveness estimates?	The EAG base-case approach slightly decreased the ICER versus pembrolizumab combination therapy and substantially increased the ICER versus pemetrexed plus platinum chemotherapy. The expected effect of informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial is unclear.
What additional evidence or analyses might help to resolve this key issue?	A scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NG122 = NICE guideline 122	

1.6 Summary of the EAG's view

The CS base-case probabilistic ICERs versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy were £5,209 and £36,025 per QALY gained, respectively. The estimated EAG base-case ICERs (probabilistic) versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, based on the EAG preferred assumptions highlighted in Section 6.1, were £5,535 and £42,230 per QALY gained, respectively. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NICE guideline 122 (NG122) and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

In conclusion, there is large remaining uncertainty about the effectiveness and cost-effectiveness of selpercatinib, which can be partly resolved by the company by conducting further analyses. This includes providing outcomes of a state transition model (STM) to assist in verifying the plausibility of the propensity score matching (PSM) extrapolations, more transparency/details concerning the choice of parametric survival curves, scenario analyses exploring potential waning of the selpercatinib treatment effect, and a scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Mature long-term selpercatinib PFS and OS data would help to reduce the uncertainty surrounding the extrapolated survival data. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of selpercatinib compared with relevant comparators.

Table 1.19: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
CS base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (1-Error in calculation of total subsequent treatment costs)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (2-Inconsistency subsequent treatment after selpercatinib)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,662	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,987	[redacted]	[redacted]
Matter of judgement (3-PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,478	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,859	[redacted]	[redacted]
Matter of judgement (4-Subsequent treatments based on NG122 and expert oncologist)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,467	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,347	[redacted]	[redacted]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,230	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,535	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for willingness-to-pay (WTP) of £36,000 per QALY
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NG122 = NICE guideline 122; PD = progressed disease; QALY = quality adjusted life year; TA = Technology Appraisal

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated advanced *RET* fusion-positive NSCLC.	Treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC who require systemic therapy.	The evidence presented in this submission is for patients with non-squamous histology. This population is in line with the LIBRETTO-001 Phase 1/2 trial (the clinical trial comprising the clinical evidence base for selpercatinib in the submission), where no treatment-naïve patients in the LIBRETTO-001 trial had squamous histology. RET fusions rarely occur in NSCLC tumours with squamous histology, which was acknowledged by the Committee in the previous evaluation for selpercatinib.	No evidence has been presented for patients with squamous histology, so the clinical effectiveness and cost-effectiveness in this subgroup is unknown.
Intervention	Selpercatinib	Selpercatinib 160 mg BID.	As per the NICE final scope.	The intervention is in line with the NICE scope.
Comparator(s)	For people with untreated advanced RET fusion positive NSCLC: • Pralsetinib (subject to ongoing NICE appraisal ID3875) For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy	Pembrolizumab with pemetrexed and platinum chemotherapy. Pemetrexed and platinum chemotherapy.	As discussed above, the target population has been restricted to patients with non-squamous histology, in line with the population of the LIBRETTO-001 study. As a result, comparators presented in the pre-invitation scope relevant to the squamous population will not be included in the submission. This approach was discussed and accepted by the Committee for the selpercatinib	The company argue that the excluded comparators (pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment) are not used frequently enough according to clinical expert

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) with (following cisplatin-containing regimens only) or		evaluation for pre-treated NSCLC patients. In line with clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication, feedback from UK clinical experts consulted by Eli Lilly as part of the evaluation process indicated that, of treatments available for patients with untreated, advanced, non-squamous NSCLC, patients with a positive *RET* status are most commonly treated with either pemetrexed with platinum-based chemotherapy OR pembrolizumab plus pemetrexed with platinum-based chemotherapy. As such, these are the only comparators considered relevant to this submission. Pralsetinib is not considered a relevant comparator in this population as it has not received a positive recommendation from NICE, and therefore is not considered part of routine practice.	opinion. This is despite these treatments being recommended by the NICE guideline NG122. A stronger rationale is required for a decision that could have a profound effect on clinical and cost-effectiveness.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Atezolizumab • Pembrolizumab with carboplatin and paclitaxel (who need urgent clinical intervention) For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel			
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • TTD	Primary: • ORR Secondary: • DOR • PFS • OS	As per the NICE final scope.	The outcomes reported are in line with the NICE scope apart from the addition of DOR.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment

	• Adverse effects of treatment
	• HRQoL.
		• Time to treatment discontinuation
		• HRQoL:
		  • EORTC QLQ-C30
		• Safety outcomes:
		  • AEs		

Economic analysis	The cost-effectiveness of treatments is expressed in terms of incremental cost per QALY. The time horizon for estimating cost-effectiveness was set at a lifetime horizon to sufficiently reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost-effectiveness analysis has been conducted for selpercatinib versus relevant comparators. As per the NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALYs. Costs are considered from the perspective of the NHS and PSS. A lifetime horizon is used to capture all costs and benefits associated with selpercatinib and its comparators.	In line with the NICE final scope.	Consistent with the scope.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • tumour histology (squamous or non-squamous), and	The following subgroup analysis are considered: Subgroups analyses in *RET* fusion-positive advanced	PD-L1 status was not collected in the pivotal LIBRETTO-001 trial, therefore subgroup analyses of patients based on PD-L1 expression were not able to be performed. In addition, as all treatment-naïve patients with advanced	The EAG accepts the lack of feasibility of PD-L1 and tumour histology subgroup analysis, notwithstanding the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• level of PD-L1 expression.	NSCLC patients with brain metastases.	*RET* fusion-positive NSCLC enrolled in the LIBRETTO-001 trial had non-squamous histology, subgroup analyses by tumour histology were similarly not able to be performed. Subgroup analyses were conducted in patients with brain metastases. It has been found that approximately 50% of patients with *RET* fusion-positive NSCLC experience brain metastases therefore subgroup analyses in this population were performed.[2]	evidence being entirely in the non-squamous population. The EAG also considers that the brain metastases subgroup analysis might provide some evidence to suggest brain metastases should have been considered as a treatment effect modifier.

Based on Table 1 of the CS[3]

AEs = adverse events; BID = twice daily; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core 30; HRQoL = health-related quality of life; N/A = not applicable; NG122 = NICE guidelines 122; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PAS = Patient Access Scheme; PD-L1 = programmed death receptor ligand 1; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RET = rearranged during transfection; TTD = time to treatment discontinuation

2.1 Population

The population defined in the scope is: *"Adults with untreated advanced RET fusion-positive non-small cell lung cancer (NSCLC)"*.[4] The population in the company submission[3] (CS) is limited to *"Treatment-naïve patients with advanced non-squamous RET fusion-positive NSCLC who require systemic therapy".*

EAG comment:

- The phrase "who require systemic therapy" is added to the definition of the scope population in the company's decision problem (Table 2.1). Therefore, the Evidence Assessment Group (EAG) asked for the implications that this might have for the characteristics of the patients and standard care i.e., comparators as well as how would those who require systemic therapy be differentiated from those who do not. In response to the clarification letter the company stated that *"This wording was added to reflect the anticipated marketing authorisation for the indication under appraisal. Lilly can now confirm that the description of the population in the decision problem should be updated to align with the anticipated label: 'Selpercatinib as a monotherapy is indicated for the treatment of adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor'….As outlined in Section B.1.2.2. of the Company Submission, RET-fusion positive patients are identified via genetic testing. Specifically, next generation sequencing (NGS) can be completed by Genomics Hubs, which allows a panel of genetic mutations, rearrangements and fusions (including RET fusions) to be identified". The EAG interprets this response to mean that the phrase, "who require systemic therapy"* is no longer part of the definition of the population.
- The company stated that *"The evidence presented in this submission is for patients with non-squamous histology"* (Table 2.1). In the clarification letter, the EAG asked if the company could confirm that the population in the decision problem should be amended accordingly, to which the company responded as follows: *"As noted in Section B.1.2.1 of the Company submission, RET fusions are most commonly seen in adenocarcinoma, but have also been reported in mixed adenosquamous histology. The relative rarity of RET mutations with a squamous histology is supported by a recent retrospective observational study published by Hess 2021, which found that patients exhibiting metastatic NSCLC with RET mutations were more likely to have non-squamous histology than the general NSCLC population. As such, whilst squamous histology was not an exclusion criterion for enrolment in the LIBRETTO-001 trial, owing to the rarity of RET-fusion positive squamous histology, no squamous patients were enrolled into the SAS1 population. This is reflected by the Committee conclusions in a recent NICE appraisal, TA760 for selpercatinib in previously treated RET fusion-positive advanced NSCLC. In this submission, no evidence on the treatment of squamous tumours was presented owing to only a very small number of squamous patients enrolling in the efficacy set. However, the NICE Committee noted that the marketing authorisation for selpercatinib in this indication does not differentiate between patients with squamous and non-squamous histology. Furthermore, the Committee acknowledged that the RET-fusions positive squamous population is very small, and heard from clinical experts that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. As such, the Committee agreed that the recommendations would apply to both squamous and non-squamous advanced NSCLC. Therefore, Lilly can confirm that a broad recommendation, unrestricted by squamous histology, is being sought for selpercatinib in the first-line setting, and therefore that the population in the decision problem should not be amended from the wording currently provided".* Notwithstanding the advice from clinical experts, the EAG does not think it is ideal that recommendations are applied to

populations other than those on whom selpercatinib has been trialled and therefore this is a key issue.

- The company have not provided any comparative evidence, including via an indirect treatment comparison (ITC) or network meta-analysis (NMA), in the rearranged during transfection (RET) fusion-positive population.[3] Nor did they adjust for RET fusion status in the ITC (see Section 3.4.1). However, there is a randomised controlled trial (RCT) with a comparison to the two comparators in the decision problem in process (see Section 3.2.8). Therefore, lack of comparative evidence in the index population constitutes a key issue.

2.2 Intervention

The intervention is selpercatinib 160 mg twice daily (BID).

EAG comment: The intervention is in line with the scope.

2.3 Comparators

The comparators listed in the scope [4] are specified by histology, non-squamous or adenocarcinoma, and programmed death receptor ligand 1 (PD-L1) status. However, the company only lists two comparators, regardless of histology and PD-L1 status:

- pembrolizumab with pemetrexed and platinum chemotherapy
- pemetrexed and platinum chemotherapy

EAG comment:

- Pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment were not included as comparators, although they were all included in the scope, as well as the NG122 care pathway. Therefore, the EAG requested adequate justification for these discrepancies, citing objective evidence of standard care for the non-squamous advanced NSCLC population. In response to the clarification letter the company stated that, "*Pemetrexed with platinum chemotherapy is included in the NICE scope for patients with non-squamous histology. 'Pemetrexed in combination with a platinum drug (carboplatin or cisplatin)' is included in the list of comparators for patients with adenocarcinoma. As outlined in Section B.1.2.1 of the Company Submission, adenocarcinoma and large cell undifferentiated carcinoma are considered together under "non-squamous" histology. As outlined in Section B.1.2.2 of the Company Submission, comparator choice was informed by feedback received from expert oncologists practicing in the NHS to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected. The expert oncologist consulted noted that immunotherapies alone are less effective in RET-fusion positive patients and therefore their use in clinical practice is limited. The limited efficacy of mono-immunotherapy in these patients is supported by the conclusions of a real-world evidence study conducted by Offin et al. in 2019, which found median PFS in RET-fusion positive NSCLC patients treated with mono-immunotherapy was just 3.4 months (95% CI, 2.1 to 5.6 months). The authors concluded that RET-fusion positive lung cancers may be less likely to be highly responsive to immunotherapy as compared with other cancers, and noted that this was reflected in the overall poor outcomes observed. In addition to this, the expert oncologist consulted by Lilly emphasised that UK clinicians are typically keen to avoid use of mono-immunotherapies as first line options in RET-fusion positive patients, particularly considering the associated toxicities that can occur if a tyrosine kinase inhibitor (TKI) is subsequently provided in the second line. Based on this, the expert feedback received from Lilly was that patients in UK clinical practice*

are typically treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab in combination with pemetrexed plus platinum chemotherapy, as these have demonstrated improved efficacy in the RET fusion-positive population. This feedback, and the subsequent comparator choice, is aligned with that received from clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication (TA812). As such, pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy are considered the only relevant comparators to selpercatinib in this indication". The EAG also asked the company to conduct all effectiveness analyses, whether by ITC (by using individual patient data (IPD)) or NMA or combination (as in the CS), and cost-effectiveness analyses including all comparators in the scope and the NG122 care pathway. The company replied that, "*Lilly consider that pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy represent the only relevant comparators to selpercatinib in this submission. As such, neither an NMA nor cost-effectiveness analysis including the other treatments named in the NICE scope have been conducted".* The EAG is not satisfied with this response. The company have rejected NICE-recommended comparators based on clinical opinion and an arbitrary selection of evidence.

- A better approach would be to have included all the NICE scope comparators and tested the relative efficacy rigorously. In fact, the company have included the trial used to inform the NICE appraisal of atezolizumab plus bevacizumab, carboplatin and paclitaxel (Technology Appraisal (TA) 584) cited in NG122, IMPower 150, in the NMA (see Section 3.3), but not provided any results from this comparison.[5] The trials used to inform the NICE appraisals of pembrolizumab monotherapy (TA531)[6] and atezolizumab monotherapy (TA705)[7] cited in NG122, KEYNOTE-024 and IMPower 110 respectively were excluded from the NMA because "*Included PD-L1 ≥50% data only*" (see Table 28 in Appendix D).[8] There is no NICE appraisal associated with platinum doublet chemotherapy, but four trials of paclitaxel plus platinum induction are included in the NMA, all by comparison with the addition of bevacizumab and then via a connection to pemetrexed plus platinum chemotherapy (see network diagrams in Section 3.4). Any effectiveness estimate based on the NMA would probably then have to be adjusted based on the effect of the addition of maintenance pemetrexed, which is included in NG122 based on TA190.[9] The possibility therefore remains that there exist comparators that are either more effective than and/or cost effective versus selpercatinib and therefore this remains a key issue.

2.4 Outcomes

The NICE final scope[4] lists the following outcome measures (company decision problem in brackets):

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate (overall response rate (ORR))
- Time to treatment discontinuation (TTD)
- Adverse effects of treatment
- Health-related quality of life (HRQoL) (European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30))

The company also added duration of response (DOR).

EAG comment:

- In the clarification letter, the company were requested to explain the choice of HRQoL and the fact that European Quality of Life-5 Dimensions (EQ-5D) was not included, to which they responded, *"The phase I/II LIBRETTO-001 study collected EORTC QLQ-C30 data to address an exploratory*

objective: 'To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL)'. The study population was not restricted to one tumour type, like NSCLC, where more specific questionnaires would be available. EORTC QLQ-C30 is well established cancer PRO tool that is broadly used and validated, and it represents one of the most commonly used measures in cancer. As such, Lilly consider the EORTC QLQ-C30 data adequately and appropriately capture HRQoL for patients in the LIBRETTO-001 trial…. Generic measures of health, such as EQ-5D, are available and can be used to inform economic evaluation. However, they have been found to be inappropriate or insensitive for some medical conditions and for cancer in particular where it is less sensitive to cancer-specific symptoms. In contrast, as outlined in response to Part a) of this question, changes from baseline in disease-related symptoms and HRQoL are well addressed by the EORTC QLQ-C30. In addition, the LIBRETTO-001 study was a Phase I/II exploratory basket trial, including other solid tumours and was therefore not designed as a randomised trial or large confirmatory trial, such as those for Phase 3. As such, collection of EQ-5D data was not included in the trial design in order to lessen the burden of data reporting for health care providers and patients. However, the LIBRETTO-431 study uses more questionaries including both EORTC QLQ-C30 and EQ-5D". In view of this response, the EAG agrees that the use of EORTC QLQ-C30 in the trials was appropriate. However, the company's argument that EQ-5D was not used due to its lower sensitivity to cancer-specific symptoms is rather undermined by the fact that EQ-5D has been used in LIBRETTO-431.

- The company were also requested to justify the use of the outcome 'duration of response', given that this is not in the NICE scope and that it may overlap with other outcomes. The company responded by stating that, *"Overall response rate (ORR) was the primary endpoint in LIBRETTO-001, with objective response rate and best overall response also being measured. Improved response rate and reductions in tumour size may lead to the relief of symptoms and help to preserve HRQoL. Therefore, duration of response was also considered as an important outcome because by maintaining the response of the tumour to treatment and inducing shrinkage, relief from disease progression may be maintained for longer and patients may experience improved OS. However, results for this outcome were provided as supportive data only and did not inform the economic model"*. Given that duration of response does not inform the economic model, the EAG will not present results relating to 'duration of response' in this report.

2.5 Other relevant factors

None.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature search was conducted to identify clinical trial evidence on the efficacy and safety of selpercatinib and relevant comparators in untreated patients with NSCLC. Full details of the search strategies, study selection process and results were reported in Appendix D.[8]

3.1.1 Searches

The following section contains a summary and critique of literature searches related to clinical efficacy and safety presented in the CS.[3, 8] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The CS was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[12]

Appendix D of the CS provided details of the literature searches conducted for the systematic literature review (SLR) of clinical efficacy and safety.[8] The searches were conducted in January 2016 (SLR1), then updated in June 2018 (SLR2), July 2020 (SLR3), July 2021 (SLR4) and April 2022 (SLR5). Two additional searches were conducted to incorporate new comparator interventions in June 2018 (SLR2: additional comparators) and August 2020 (SLR3b). The additional comparator interventions were then included in subsequent update searches. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for the clinical effectiveness systematic review (as reported in the company submission).

Resource	Host/Source	Date Ranges		Dates searched	
Electronic databases					
MEDLINE and MEDLINE In-Process, E-Pub Ahead of Print	Ovid	SLR1 SLR2 SLR2 targeted SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR2T SLR3 SLR3b SLR4 SLR5	12/01/2016 13/06/2018 13/06/2018 29/07/2020 27/08/2020 30/07/2021 20/04/2022
Embase	Ovid	SLR1 SLR2 SLR2 targeted SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR2T SLR3 SLR3b SLR4 SLR5	12/01/2016 15/06/2018 15/06/2018 29/07/2020 27/08/2020 30/07/2021 20/04/2022
Evidence-based medicine reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of	Not reported	SLR1 SLR2 SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR3 SLR3b SLR4 SLR5	12/01/2016 18/06/2018 30/07/2020 27/08/2020 30/07/2021 20/04/2022

Resource	Host/Source	Date Ranges	Dates searched
Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database)			
Clinical trials registries			
ClinicalTrials.gov		Not reported	Not reported
International Clinical Trials Registry Platform		Not reported	Not reported
Conference proceedings			
American Association for Cancer Research (AACR)	Embase (Ovid) AACR website	SLR2 2014 –Q2 2022 SLR3-SLR5	SLR2 23/07/2018 June 18-April 2022
The European Lung Cancer Conference (ELCC)	Embase (Ovid) Embase (Ovid) ELCC website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
World Conference on Lung Cancer (WCLC)	Embase (Ovid) Embase (Ovid) WCLC website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
European Society for Medical Oncology (ESMO)	Embase (Ovid) Embase (Ovid) ESMO website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
ESMO Immuno Oncology Congress	Embase (Ovid)	SLR2 2014 –Q2 2022	SLR2 23/07/2018
American Society for Clinical Oncology (ASCO)	Embase (Ovid) Embase (Ovid) ASCO website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
HTA organisation websites			
National Institute for Health and Care Excellence (NICE)		Not reported	Not reported
Reference lists of any identified systematic reviews and meta-analyses published in the last year were searched for further studies of interest.			

EAG comment:

- The CS provided details of the literature searches for the EAG to appraise.[3, 8]

- A good range of databases and relevant conference proceedings were searched.
- Full details of the database search strategies, including the database name, host platform, and date searched, were provided. The database date ranges were not reported.
- Details of the conference proceedings searched were provided. The search terms used, URL links, specific date of searches, and results, were reported.
- The NICE website was searched for published assessments and guidelines. Full details of this search were not provided: search date, search terms, and number of records retrieved. Full details of the NICE website search were provided in response to the EAG clarification letter.[13]
- The clinical trials registries www.ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) were searched to identify ongoing clinical trials. Keywords were reported, but there were no details of the date searched and the number of records retrieved. Details of the dates searched for SLR4 and SLR5 were provided in the response to clarification.[13]
- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE). There were no language or date limits.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-S reporting checklist recommends.[14] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[15]
- Study design search filters for RCTs were included in the search strategies. The search filters used were not cited, as current practice recommends.[14] It was not clear if the RCT filters were validated published filters or were devised by the review team.
- Separate searches for safety were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify safety data. Ideally, searches for adverse events should be carried out alongside efficacy searches.[16]
- The original Embase clinical evidence search strategy SLR1, and updates SLR2 and SLR3 were more precise than the equivalent MEDLINE search strategies, using focussed EMTREE, searching in the title field only, and using the frequency operator to search the abstract field.
- Two targeted searches were conducted (SLR2 targeted and SLR3b) when new comparator drugs were introduced to the search strategies.
- The SLR3b MEDLINE search strategy reported in Table 5 was incorrect, replicating the MEDLINE SLR3 strategy reported in Table 4. The strategy was correctly reported in Table 6.
- The MEDLINE, Embase and EBMR search strategies for the final two update searches (SLR4 and SLR5) were different to those search strategies used for the original searches and previous update searches (SLR1, SLR2, SLR2: targeted, SLR3 and SLR3b). Consequently, these final two searches were not updates, but rather 'new' searches.
- The Population search facet in the SLR4 and SLR5 searches was more precise than that used in the original search, which searched broadly for NSCLC. The more precise Population facet searched for NSCLC combined with search terms for 'advanced/metastatic' AND 'first line therapy'. Another element of the search strategy included a Population facet with additional search terms for 'RET fusion'.

- In the methods Section (see Appendix D.1.1) it was reported that '*search strategies did not specify treatment line'*, but the SLR4 and SLR5 update searches did include a search line for 'first line treatment' in the Population facet.[8]
- The SLR4 and SLR5 update searches included an age limit for 'Adults' that was not included in the previous searches.
- Different RCT filters were used in the SLR4 and SLR5 search strategies to those used in the original SLR1 search strategies (and updates, SLR2 and SLR3), and as the filters were not cited, it was not clear where they were derived from.
- In response to clarification questions about the differences in the search strategies used for SLR4 and SLR5, as listed above, the company explained that *'SLR1 and SLR2 were conducted from a Global perspective, with objectives and scope broader than the current decision problem. From SLR3, the search strategy was narrowed to make it more robust and specific; the addition of the search terms and age limits reduced the number of irrelevant hits produced. Fundamentally, the search strategy remained broadly similar throughout all of the relevant updates, but with amendments made for the last two updates to make them specific, directed and optimised for the population of interest. Lilly do not consider that these adjustments will have excluded any relevant data from the search results.'*[13]
- There were two elements to the SLR4 and SLR5 search strategies with separate results. One of the elements combined the search facets for Population, Interventions and RCT filter, but incorrectly only included search line #52 (the first line of the RCT filter), rather than search line #54 (the complete RCT filter) (Table 7, Table 8, Table 14 and Table 15).
- The date limit field tag 'date created (dc)' was used in the SLR4 and SLR5 update searches in MEDLINE and Embase, when it is only available in Embase; the equivalent field in MEDLINE is 'entry date (ed)'.
- The search line for 'first line/untreated therapy' was suboptimal, as it did not include truncation, proximity operators, and a number of the search terms were redundant.
- EBMR includes several different resources, but the CS only reported the results of searches from the Cochrane Central Register of Controlled Trials (CENTRAL).
- The host interface for EBMR was not reported. Although not reported, it appears that the SLR1 and SLR2 EBMR search strategies (Table 16 and Table 17) were conducted via the Cochrane Library, rather than via EBMR in Ovid. Search strategies for SLR3, SLR4 and SLR5 were conducted via Ovid EBMR.
- The EBMR search strategy for SLR3 was reported incorrectly, presenting duplicate search lines, and inaccurate set combinations (Table 18).
- The MEDLINE, Embase and EBMR search strategies for the final two update searches (SLR4 and SLR5) were identical, incorrectly using MeSH in Embase and EBMR.
- As the same search strategy was used for the SLR4 and SLR5 update searches in MEDLINE, Embase and EBMR, the RCT filter was included in the CENTRAL search. It is not necessary to include an RCT filter when searching a database of trials, as this may result in unnecessarily restricting the results retrieved.
- The last 40 search lines from line #24 onward were missing from the MEDLINE SLR5 search strategy (Table 8). The full MEDLINE SLR5 search strategy was provided in response to the EAG clarification letter.[13]

3.1.2 Inclusion criteria

A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for advanced RET fusion-positive NSCLC who require systemic therapy, including treatment-naïve adults.

The original SLR was conducted in January 2016, and there were four subsequent updates in June 2018, July 2020, July 2021 and April 2022. The eligibility criteria used in the decisions for inclusion/exclusion into the SLR are presented in Table 3.2. For brevity this shall also be referred to as the SLR 'protocol' in the report.

Table 3.2: Eligibility criteria (protocol) used for selection of evidence for the company's SLR

Study characteristics	Eligible	Ineligible
Population	Adult patients (≥18 years old) with locally advanced or metastatic non-squamous NSCLC (stage IIIB or IV) receiving first line and first line to progression	Children and adolescents
Intervention	Selpercatinib (Loxo-292) Pralsetinib (Blu667) Afatinib Bevacizumab Carboplatin Cisplatin Crizotinib Docetaxel Erlotinib Gefitinib Gemcitabine Nab-Paclitaxel Nivolumab Paclitaxel Pembrolizumab Pemetrexed Ramucirumab Atezolizumab Durvalumab Ipilimumab Tremelimumab Combinations of the above.	Studies that do not include any of the interventions of interest in at least one study arm. Studies comparing an intervention of interest with nonpharmacological treatments e.g., surgery, complementary therapy.
Comparators	Any active systemic therapy, placebo, best supportive care, or no treatment.	Studies comparing an intervention of interest with non-pharmacological treatments e.g., surgery, complementary therapy.
Outcomes	At least one of the following outcomes: • PFS • OS • Safety (Grade 3–4 AEs)	Studies that do not report at least one of the outcomes of interest
Study Design	RCT[b] in first-line NSCLC. Language restriction to English. Systematic reviews.	Single-arm trials in patients without RET alterations. Prospective observational studies. Preclinical studies. Prognostic studies.

Study characteristics	Eligible	Ineligible
		Case reports. Commentaries and letters (publication type). Consensus reports. Non-systematic reviews. Registry studies. Case-control studies. Cross-sectional surveys. Retrospective studies.
Time frame	SLR1: Database inception to 12 January 2016 SLR2: 2016 to 13 June 2018 SLR3: 2018 to 29 July 2020[c] SLR4: 2020 to 30 July 2021 SLR5: 30 July 2021 to 20 April 2022[d]	None
Other considerations	Studies that included head-to-head comparisons of at least two of the treatments listed (or placebo) were eligible for inclusion.	Studies of monotherapies were not considered for inclusion.

Based on Table 25, CS Appendix D[8]
[a] Studies including only a mutation positive-specific population (EGFR+, ALK+) were excluded.
[b] RCTs with mixed histologic populations were included when results specifically for the non-squamous population were reported, an exception was made for CHECKMATE 227, KEYNOTE-042 and KEYNOTE-024 where efficacy data for squamous population were extracted.
[c] Additional search strategy to identify selpercatinib and pralsetinib (not in scope for the SLR1 or SLR2) was run on 27 August 2020 (SLR3b).
[d] Due to search string constraints in the EMBR databases, the time frame for EBMR will be restricted to January 2021-present in the searches.
AE = adverse events; ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; RET = rearranged during transfection; SLR = systematic literature review.

EAG comment:

- The SLR protocol (Table 3.2) only appeared to include RCTs as the source of primary research findings, even though the company's own research work on selpercatinib (LIBRETTO-001 and LIBRETTO-321) did not involve RCT data. In the context of the CS,[3] a major purpose of the SLR is to ensure that all relevant data have been found and are available for inclusion in the clinical effectiveness section of the CS.[3] However, given the protocol wording, it would not seem possible for the LIBRETTO one-arm trials to be included in the SLR, and thus the clinical effectiveness Section.
- As a means to circumvent this, the company states in CS, Appendix D[8] that, '*Data in patient populations with RET fusions were expected to be sparse and therefore, single-arm trials reporting data from patients with RET fusion-positive NSCLC and data from RCTs in the wider non-squamous NSCLC population were also searched for.*' However, because this statement is not included in the protocol itself (Table 3.1) the rigour of the protocol as a pre-hoc determination of the scope and methodology of the SLR is called into question.

- As a further example, the dates of the four SLR updates are given, but no information is given on the nature of these updates. It is unclear if these updates were simply 're-runs' or if changes were made to the inclusion/exclusion criteria of the protocol on each update.
- In Section B.2.1 of the CS[3] the company stated that they included only "first-line to progression studies". The justification for this in Appendix D Section D1.1[8] is that selpercatinib is administered *"…until progression (or unacceptable toxicity)".* The company were asked to explain why the method in which selpercatinib is administered should determine the inclusion of studies of comparator treatments. The company stated that, "*As it is anticipated that selpercatinib will be administered 'until progression or until acceptable toxicity occurs' in UK clinical practice, the first line to progression treatment setting aligns more closely with the decision problem. In all studies categorised as "first line", the maximum number of treatment cycles were fixed in the study design and the number of treatment-cycles allowed in these studies varied but were limited to 6 cycles at most (see Appendix D). The "First line to progression" category included regimens where one or more treatments in the combination were allowed to be administered until progression and study regimens with fixed number of cycles and study regimens which allowed maintenance/continuation beyond "induction" were not considered comparable, even with the same drugs included. Accordingly, only studies reporting 'first line to progression' treatments were deemed relevant for inclusion in the NMA and were reported in Appendix D of the Company Submission."* The company did acknowledge that first line fixed cycle length (as opposed to until progression) treatments might be relevant to United Kingdom (UK) clinical practice, an example that is relevant to the decision problem being pembrolizumab with a 2-year stopping rule.[13] However, they claimed that *"…these treatment rules are a consequence of NICE guidance rather than the trial design themselves."*, so that *"…first line to progression studies would capture all relevant trials for the decision problem."* (p.35) In fact, the EAG notes that KEYNOTE-189 and KEYNOTE-189 Japan, two of the three trials of pembrolizumab combination with pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy included in the CS had a maximum treatment duration of 35 3-week cycles i.e., effectively a stopping rule at 2 years (see Section 3.3).[17, 18] However, treatment to progression applied up to this 2-year limit: *"…treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent".*[19] The other included trial is KEYNOTE-021, which also had a stopping rule for pembrolizumab of 2 years, and applied the same criteria for discontinuation.[20] The same criteria also apply to clinical practice, as stated in the NICE recommendation for pembrolizumab with pemetrexed plus platinum chemotherapy in TA683.[21] Therefore, the company appear to have applied this rule of only including 'treat to progression' studies unnecessarily, and regardless of the rule the inclusion of KEYNOTE-021 and KEYNOTE-189 is appropriate to the NICE scope. The company did provide a list of all first line studies that they retrieved in the SLR and, given the decision problem, the only other studies that could be relevant would be those including pemetrexed and chemotherapy and the company argue that pemetrexed would only be used in clinical practice according to NG122 as "*maintenance*". However, TA181,[22] which is cited in NG122, recommends it for induction in combination with platinum chemotherapy and the EAG notes that several of the 12 studies listed by the company as first-line studies have a pemetrexed and chemotherapy arm, including the one on which TA181 is based.[23] This seems to imply that studies have been excluded erroneously. However, the EAG also notes that pemetrexed maintenance is recommended according to TA402 following induction with pemetrexed plus platinum chemotherapy. It also appears that the combination of induction and maintenance is effectively 'treat to progression' and how pemetrexed was administered in the three included trials of pemetrexed (KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021). Therefore, it seems probable that the company is

correct that applying the 'treat to progression' criterion, although perhaps for the wrong reason, has had no impact on inclusion of studies relevant to the scope.

- The company have also been asked to state if any comparator treatments are administered for a fixed number of cycles or for a fixed time period, if so then they were asked to include studies of those treatments. The company re-stated that, "*.. limiting the NMA to include only first line to progression studies will not have excluded any data relevant to the current appraisal*." The EAG does not think that the company have answered this question satisfactorily, although this probably does not have serious implications.
- Finally, the company were asked to verify that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity'. The company stated that, "*Lilly can confirm that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity*." The EAG thanks the company for this clarification.

In conclusion, the EAG was concerned that the narrowing of the evidence base to 'first line to progression studies' based on how selpercatinib treatment might be at odds with the NICE scope and company's own decision problem and therefore might not cover the required evidence base. However, it does appear that at least for the comparators in the decision problem this is consistent with NICE guidance and therefore National Health Service (NHS) clinical practice. In principle the effectiveness of pemetrexed and platinum chemotherapy 'treat until progression' could be estimated from a combination of trials at induction only and maintenance only, but it is unclear how this might be achieved technically. It also seems unnecessary given the availability of evidence for 'treat until progression' in the form of those three included studies KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021.

3.1.3 Critique of data extraction

All abstracts were reviewed independently by two systematic reviewers using the DistillerSR® tool, according to the eligibility criteria outlined in Table 3.2 above; any differences in opinion regarding eligibility were resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full texts. The full texts were split according to the treatment line (first line, first-line to progression) and subsequently, each treatment line was considered independently for inclusion of studies and data extraction.

Sixty-six papers were initially chosen for inclusion in the SLR. As these included papers were collected for the ITC, also covering studies not involving selpercatinib, they have been described fully in Section 3.3. Only two included studies directly covered selpercatinib – LIBRETTO-001 and LIBRETTO-321- both of which were one arm trials.

EAG comment:

- As stated previously, the review protocol (Table 3.2) only appeared to specify RCTs and SLRs for inclusion. As there are no RCTs covering selpercatinib in the inclusion list, the SLR yielded no RCT data of direct relevance to the decision problem (selpercatinib versus the active comparators listed in Table 2.1).
- It is only the company's statement in the text of the appendices[8] that permits additional inclusion of, '*single-arm trials reporting data from patients with RET fusion-positive NSCLC and data from RCTs in the wider non-squamous NSCLC population',* that allows the studies from the one-arm LIBRETTO-001 and LIBRETTO-321 [24] trials to be included in the SLR. This amendment should have been reflected in the final protocol, for greater transparency. The company have been asked to comment on this, and stated that, "*At the time that the original SLR was conducted in July 2018,*

the comparator trials published in RET fusion-positive NSCLC were not of particular interest. For the update of the SLR conducted in July/August 2020, the protocol was amended in order to support selpercatinib HTA appraisals to include single arm trials for selpercatinib and pralsetinib. This reflected that both treatments were expected to have market access based on single arm clinical trials and that no RCT data were expected to be published. As such, this amendment was implemented in order that potentially relevant comparator information not be missed in the systematic review. Since the update to the SLR in July/August 2020, the single arm trials for specific RET inhibitors have been eligible for inclusion in the SLR." The EAG notes that the company response does not acknowledge the importance of presenting the most up-to-date protocol in the CS to maintain transparency.

- Despite being included in the SLR, the LIBRETTO-321[24] trial data was not presented in the clinical efficacy section of the CS[3], alongside the data from LIBRETTO-001. This issue is discussed in more detail in the next Section.

3.1.4 Quality assessment

Risk of bias assessments were carried out for all studies included in the SLR. For the first and second updates, the company stated that the risk of bias assessment was conducted in accordance with the Cochrane risk of bias tool described in the Cochrane Handbook. The company also stated that the risk of bias assessment for the third and fourth updates was conducted in line with the standards recommended by the NICE. Any single-arm trials identified vis SLR3 or SLR4 were assessed by the Critical Appraisal Skills Programme (CASP) cohort study checklist.

EAG comment: It is unclear why different RCT risk of bias criteria were used for different updates of the SLR: no rationale was provided by the company.

3.1.5 Evidence synthesis

No synthesis that was directly relevant to the decision problem (selpercatinib versus the active comparators listed in Table 2.1) was carried out. However, data from the SLR were synthesised in the NMA, which is dealt with in Sections 3.4.1 and 3.4.2.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In the CS,[3] the company considered only one study - LIBRETTO-001 - which provided data on the efficacy and safety of selpercatinib. An overview of LIBRETTO-001 is included in Table 3.3.

EAG comment:

- Despite being included in the SLR, the LIBRETTO-321[24] trial data was not presented in the clinical efficacy section of the CS[3], alongside the data of LIBRETTO-001. The reasons for this are not provided by the company. The study appears eligible as it reports objective response rate (ORR) in RET fusion-positive NSCLC patients with advanced disease, where a subgroup (n=8) is treatment naïve. The company responded to the EAG request for clarification as follows: *"At the time that data extraction was ongoing for the clinical SLR, no results from the LIBRETTO-321 trial were available. As such, no data were extracted, but the first trial disclosure were captured in SLR5 from a congress abstract. A full manuscript was subsequently published after the SLR5 search date. The LIBRETTO-321 trial was conducted in China and recruited patients from China only. As noted in response to Question A17) above, there are known differences for the Asian race in NSCLC. As such, the generalisability a fully Asian cohort of patients to UK clinical practice is limited. In addition, at the time of the latest data cut off (March 2021), 47 patients diagnosed with RET-fusion*

positive NSCLC had been recruited, of which only 11 had their RET status confirmed. Of those with a confirmed RET status, only 8 patients were treatment naïve. Therefore, this change led to the exclusion of relatively immature data from only 8 patients, the results of which are anticipated to have limited applicability to the UK. Based on this, Lilly maintain that the amendment made was appropriate and did not lead to the exclusion of any relevant data". The EAG does not agree that LIBRETTO-321 should have been excluded as ethnicity was not an exclusion criterion on the review protocol (Table 3.2). Therefore LIBRETTO-321[24] trial results that are relevant to the decision problem (in the treatment-naïve (n=8) sub-group) have been added into Section 3.2 of this report.

- Randomised controlled trial data would be much more useful to this appraisal, and so it might have been prudent for the company to have delayed evidence submission until their ongoing RCT (LIBRETTO-431) yields data. Section B.2.10 of the CS[3] states: *"Results for LIBRETTO-431 are expected in December 2023. It is not anticipated for any data from this trial to become available during the course of this evaluation."* The company were asked to provide the earliest date by which an interim analysis from the randomised LIBRETTO-431 trial might be available, and the outcomes that will be presented. The company responded by stating that:[13] *"The interim analysis will be event driven and will be conducted when approximately* [redacted] *events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in* [redacted]*, with results expected to be available from* [redacted]*."* The EAG have therefore identified this lack of RCT evidence in the RET fusion-positive population as a key issue (see Section 3.2.8).

3.2.1 Details of the included trials

3.2.1.1 LIBRETTO-001

LIBRETTO-001 is an ongoing multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET fusion-positive NSCLC tumours. The patient population includes patients >12 years of age with a locally advanced or metastatic solid tumour, who fulfil one or more of the following criteria:

- progressed on standard therapy
- were intolerant to standard therapy
- were patients for whom no standard therapy exists
- weren't candidates for standard therapy
- would be unlikely to tolerate or derive significant clinical benefit from standard therapy
- declined standard therapy.

Patients are screened for eligibility based on the criteria presented in Table 3.3.

Table 3.3: Clinical effectiveness evidence

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[25]
Study design	LIBRETTO-001 is a multicentre, open-label, single-arm, Phase I/II study that is ongoing. The trial is demarcated into two parts: Phase I (dose escalation) and Phase II (dose expansion).
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g. NSCLC, thyroid, pancreas or colorectal), *RET*-MTC and other tumours with RET activation, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator were not

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[25]		
	candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and have an ECOG score of ≤2 or a LPS of ≥40%. As of 15 June 2021, N=796 patients had been enrolled onto the trial, of which N=356 were *RET* fusion-positive NSCLC patients, N=69 were treatment-naïve patients (SAS1 population). **Treatment-naïve *RET* fusion-positive NSCLC patients are the focus of this submission.**		
Intervention(s)	Selpercatinib, once or BID, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study.		
Comparator(s)	N/A – LIBRETTO-001 is a single arm trial		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use in the model	LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC.		
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • PFS • OS • HRQoL: • EORTC QLQ-C30 Safety outcomes: • AEs		
All other reported outcomes	DOR		

Based on Table 4, CS[3]
AEs = adverse events; BID = twice daily; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; HRQoL = health-related quality of life; LPS = Lansky Performance Score; MTC = medullary thyroid cancer; N/A = not applicable; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection

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

Patients were subsequently enrolled into one of five Phase II cohorts to better characterise the safety and efficacy of selpercatinib in patients with specific abnormalities in RET. Classification into cohorts was based on tumour type, type of RET alteration and prior treatment (Table 3.4).

Table 3.4: LIBRETTO-001 patient cohorts: only Cohort 2 is relevant to this report

Patient cohort	Description
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy, including *RET* fusion-positive NSCLC.
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy, **including treatment-naïve *RET* fusion-positive NSCLC (SAS1 population).**
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib.
Cohort 4	*RET*-mutant MTC without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity.
Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample.
Cohort 6	Patients otherwise eligible for Cohort 1 to 5 but who discontinued another selective *RET* inhibitor(s) due to intolerance are eligible with prior Sponsor approval.

Based on Table 5, CS[3]
CS = company submission; DNA = deoxyribonucleic acid; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection

Only a subset of patients in the LIBRETTO-001 trial are consistent with the population of relevance for this submission: 'treatment-naïve patients with advanced RET fusion-positive NSCLC who require systemic therapy', referred to as the Supplemental Analysis Set 1 (SAS1) or SAS1 population. These make up 69 of the 796 participants in the trial cohort and form cohort 2 in Table 3.4. In line with the decision problem for this submission, only results for the clinical effectiveness of selpercatinib in the 69 treatment-naïve patients with RET fusion-positive NSCLC (Cohort 2) will be included in this report.

Individual patients continued selpercatinib dosing at 160 mg BID in 28-day cycles until progressive disease (PD), unacceptable toxicity or other reasons for treatment discontinuation. The primary endpoint for the Phase II portion of the trial was ORR using RECIST v1.1. Secondary endpoints included DOR, PFS and OS, whilst the safety, tolerability and pharmacokinetic (PK) properties of selpercatinib were also considered.

EAG comment: The dose of selpercatinib is given as 160 mg BID. For other indications, the dose may be reduced for any participants weighing <50 kg. The company was asked if the dose of 160 mg BID was amended for any participants weighing <50 kg in the LIBRETTO-001 trial. If not, the company was asked to provide a rationale. If it was amended, the company was asked to clarify the number of participants affected. The company responded by stating that, "*In LIBRETTO-001, there were five patients with weight <50 kg at baseline, all of whom received 160 mg BID. Starting doses for patients in LIBRETTO-001 are presented in Table 4* [Table 3.5 below] *and were the doses used in the economic model. Weight was not a criterion for determining the starting dose, owing to LIBRETTO-001 being a Phase I/II study with a Phase I 'dose finding' phase which included dose escalation. As presented in Table 32 of the Company Submission, dose reductions were primarily due to the occurrence of adverse events. Drug dosage modifications and the reasoning for these modifications in the SAS1 population of the LIBRETTO-001 trial specifically are presented in Table 5* [Table 3.6 below]. *As shown, adverse events represented the majority of reasons for modifications. A total of* [redacted] *patients started on a lower*

dose of 80 mg BID, and this was due to the Phase I 'dose finding' nature of LIBRETTO-001. The company was also asked to confirm that the dosing in the economic model is precisely that in the LIBRETTO-001 trial. If not, the company was asked to describe any discrepancies and discuss the implications. The company stated that, "*Lilly can confirm that the dosing scheduled considered in the economic model was the same as in the LIBRETTO-001 trial."* The EAG appreciates the clarity of these responses and is satisfied with the information provided.

Table 3.5: Starting doses of patients in LIBRETTO-001

Dose (mg, twice daily), n (%)	SAS1 population (N=69)
160	[redacted]
120	[redacted]
80	[redacted]
40	[redacted]
All	[redacted]

Based on Table 4, Company response to clarification letter[13]
SAS1 = Supplementary Analysis Set 1

Table 3.6: Study drug dosage modifications in LIBRETTO-001

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

Based on Table 5, Company response to clarification letter[13]
SAS1 = Supplementary Analysis Set 1

A summary of the methodology and trial design of LIBRETTO-001 is presented in Table 3.7 below.

Table 3.7: Summary of LIBRETTO-001 trial methodology

Trial name	**LIBRETTO-001**[25]
Location	A total of 85 investigational study sites across 16 countries worldwide have participated to date: United Kingdom, Canada, United States, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy, Israel.
Trial design	A multicentre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET-alterations.
Eligibility criteria for participants	**Inclusion criteria:** At least 18 years of age (for countries and sites where approved, patients as young as 12 years of age could be enrolled). Patients with a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy or declined standard therapy. For patients enrolled into the Phase II dose expansion portion of the study, evidence of a RET gene alteration in the tumour (i.e., not just blood), was required. ECOG performance status of 0, 1, or 2 (age ≥16 years) or LPS ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. **Exclusion criteria:** Phase II Cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of selpercatinib. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment (with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least four weeks prior to the first dose of study treatment). Any unresolved toxicities from prior therapy greater than NCI CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy. Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis or untreated spinal cord compression (unless neurological symptoms and CNS imagine are stable and steroid dose is stable for 14 days prior to first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery). Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on at least 2/3 consecutive ECGs and mean QTcF >470 msec on all three ECGs during screening.

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

	Therapeutic monoclonal antibodies. Drugs with immunosuppressant properties. Medications known to be strong inhibitors or inducers of CYP3A4 (moderate inhibitors/inducers could be taken with caution. If patients received strong CYP3A4 inhibitors/inducers, then the Sponsor was consulted to determine whether to stop selpercatinib or remove the patient from the study). Herbal products, such as St John's wort, which could decrease the drug levels of selpercatinib. Investigational agents (other than selpercatinib). No new, alternative systemic anticancer therapy was allowed prior to documentation of PD. The concomitant use of PPIs was prohibited, and patients were to discontinue PPIs one or more weeks prior to the first dose of selpercatinib. Histamine type-2 blocking agents were required be administered only between 2 and 3 hours after the dose of selpercatinib Antacids e.g., aluminium hydroxide/magnesium hydroxide/simethicone or calcium carbonate, if necessary, were required to be administered 2 or more hours before and/or after selpercatinib.
Primary outcome	**Phase I:** Identification of the MTD and the RP2D of selpercatinib for further clinical investigation. **Phase II:** The primary endpoint was ORR based on RECIST v1.1 or RANO, as appropriate to the tumour type as assessed by IRC.
Secondary and exploratory outcomes	**Secondary endpoints:** Phase I: determination of the safety and tolerability of selpercatinib, characterisation of the PK properties and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO. Phase II: BOR, DOR, CBR, CNS ORR, CNS DOR, PFS, OS, AEs and changes from baseline in clinical safety laboratory values and vital signs, characterisation of PK properties. **Exploratory endpoints:** Determination of the relationship between PKs and drug effects (including efficacy and safety). Evaluation of serum tumour markers. Characterisation of RET gene fusions and mutations and concurrently activated oncogenic pathways by molecular assays, including NGS from tumour biopsies and cfDNA. Collection of PROs data to explore disease-related symptoms and HRQoL.
Pre-planned subgroups	The primary objective was analysed by several demographic variables for NSCLC patients enrolled in the trial: • Age (≥65 versus <65) • Sex (male versus female)

	• Race (white versus other) • ECOG (0 versus 1–2) • Metastatic disease (yes versus no) • CNS metastasis at baseline by investigator (yes versus no) The primary objective was also analysed by type of *RET* fusion partner and type of *RET* molecular assay used for NSCLC patients enrolled in the trial: Fusion partner: KIF5B CCDC6 NCOA4 KIAA1468 ARHGAP12 CCDC88C CLIP1 PRKAR1A RBPM and DOCK 1 TRIM24 Other Unknown Molecular assay: NGS on blood or plasma NGS on tumour PCR Other
Duration of study and follow-up	The study is ongoing. The first patient was treated on 9 May 2017. At the latest data cut-off of 15 June 2021, the median follow-up was 25.2 months for OS and 21.9 months for PFS for SAS1 (treatment-naïve) patients.[26] Patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity or other reasons for treatment discontinuation. Four weeks (28 days + 7 days) after the last dose of study drug, all treated patients underwent a safety follow-up (SFU) assessment. All patients were also to undergo long term follow-up (LTFU) assessments every 3 months.
Based on Table 6, CS[3]	

ACTH = adrenocorticotropic hormone; AE = adverse event; ASCO = American Society for Clinical Oncology; BID = twice daily; BOR = best overall response; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; cfDNA = circulating free DNA; CNS = central nervous system; CYP3A4 = cytochrome P450 3A4; DOR = duration of response; ECGs = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL = health-related quality of life; IRC = Independent Review Committee; LPS = Lansky Performance Score; LTFU = lost to follow-up; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; NGS = next generation sequencing; NCI CTCAE = National Cancer Institute common terminology criteria for adverse events; ORR = objective response rate; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetic; PPI = proton pump inhibitors; PRO = patient reported outcome; QD = once daily; QTcF = QT interval corrected for heart rate using Fridericia's formula; RANO = response assessment in neuro-oncology criteria; RBC = red blood cell; RECIST = response evaluation criteria in solid tumours; *RET* = rearranged during transfection; RP2D = recommended Phase II dose; SAS1 = Supplemental Analysis Set 1; SFU = safety follow-up

3.2.1.2 LIBRETTO-321

LIBRETTO-321 is an open-label, one-arm, multicentre, phase II study (NCT04280081). It has been conducted in China at 15 sites. Patients with advanced RET-altered solid tumours received selpercatinib (160 mg orally BID) in a 28-day cycle. The primary endpoint was IRC-assessed ORR; RECIST v1.1. Secondary endpoints included duration of response, CNS response, and safety.

Inclusion criteria were age of 18 years or older, with a diagnosis of advanced RET fusion-positive NSCLC. The sub-group (n=8) of relevance to this report had RET fusion-positive NSCLC (with RET status confirmed by a central laboratory) and were treatment naive. Patients were also required to have an ECOG score of 0–2 with no sudden deterioration 2-weeks prior to the first dose of selpercatinib, a corrected QT interval of 470 msec or less, and adequate hematologic, hepatic, and renal function. Exclusion criteria were: no qualified RET alteration status, prior treatment with selective RET inhibitors (including investigational selective RET inhibitors), unresolved toxicities from prior therapy worse than grade 1 according to the common terminology criteria for adverse events (CTCAE), human immunodeficiency virus (HIV), history of active hepatitis B or C, symptomatic central nervous system (CNS) tumour, concurrent use of drugs prolonging QT interval corrected for heart rate (QTc), active secondary malignancy, pregnancy, and presence of additional oncogenic drivers that could cause resistance to selpercatinib.

A summary of the methodology and trial design of LIBRETTO-321 is presented in Table 3.8 below.

Table 3.8: Summary of LIBRETTO-321 trial methodology

Trial name	LIBRETTO-321[24, 27, 28]
Location	A total of 15 investigational study sites in China.
Trial design	A multicentre, open-label, single-arm, Phase II study in patients with advanced solid tumours, including RET-alterations.
Eligibility criteria for participants	**Inclusion criteria:** At least 18 years of age. Diagnosis of advanced RET fusion-positive NSCLC. The sub-group (n=8) of relevance to this report had RET fusion-positive NSCLC (with RET status confirmed by a central laboratory) and were treatment naïve. ECOG performance status of 0, 1, or 2 with no sudden deterioration two weeks prior to the first dose of study treatment. A corrected QT interval of 470 msec or less, and adequate hematologic, hepatic, and renal function. **Exclusion criteria:** No qualified RET alteration status. Prior treatment with selective RET inhibitors (including investigational selective RET inhibitors). Unresolved toxicities from prior therapy worse than grade 1 according to the CTCAE. HIV. History of active hepatitis B or C. Symptomatic CNS tumour. Concurrent use of drugs prolonging QTc Active secondary malignancy. Pregnancy. Presence of additional oncogenic drivers that could cause resistance to selpercatinib.
Method of study drug administration	Selpercatinib was administered orally (160 mg BID) in a 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent.
Permitted and disallowed concomitant medication	**Permitted:** Not reported. **Disallowed:** Drugs prolonging QTc.
Primary outcome	The primary endpoint was ORR based on RECIST v1.1 .

Secondary and exploratory outcomes	**Secondary endpoints:** DOR. CNS response. Safety.
Pre-planned subgroups	None reported.
Duration of study and follow-up	9.7 months median follow up.

Based on Lu et al 2022[24]

BID = twice daily; CNS = central nervous system; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; CTCAE = common terminology criteria for adverse events; HIV = human immunodeficiency virus; QT = QT interval; QTc = QT interval corrected for heart rate; NSCLC =non-small-cell lung cancer; ORR = overall response rate; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection

3.2.2 Statistical analysis of the included studies

3.2.2.1 LIBRETTO-001

There were five analysis sets in LIBRETTO-001 for patients with NSCLC (Table 3.9). In line with the decision problem, only clinical effectiveness data from treatment-naïve patients with measurable disease are considered in this submission. These patients comprised the SAS1 population.

Table 3.9: LIBRETTO-001 analysis set definitions

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
Primary Analysis Set (second line)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase I and Phase II who met the following criteria: Evidence of a protocol-defined qualifying and definitive RET fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included Measurable disease by RECIST v1.1 by IA[a]. Received 1 or more lines of prior platinum-based chemotherapy. Received 1 or more doses of selpercatinib.		105
Integrated Analysis Set (second line)	All *RET* fusion-positive NSCLC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1 to 4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.		247
Supplemental Analysis Sets	All other *RET* fusion-positive NSCLC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date. SAS1 and SAS2: met PAS criteria 1, 2 and 4. SAS3: met PAS criteria 1 and 4. SAS assignment was non-overlapping; thus, SAS1 to 3 are mutually exclusive with each other.	**SAS1 (treatment-naïve; population of interest to this submission):** No prior systemic therapy.	**69**
		SAS2 (prior other systemic therapy): Received prior systemic therapy other than platinum-based chemotherapy.	[redacted]
		SAS3 (non-measurable disease): No measurable disease[b].	[redacted]
Safety analysis			
Overall Safety Analysis Set	Patients treated with selpercatinib as of a data cut-off of 15 June 2021.	**NSCLC Safety Analysis Set:** *RET* fusion-positive NSCLC	356
		RET-mutant MTC	[redacted]
		RET fusion-positive thyroid cancers	[redacted]

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
		RET fusion-positive other cancers	[redacted]
		Other cancers	[redacted]
		Total	**796**

Based on Table 7, CS[3]
[a] Patients without measurable disease who were enrolled in Phase I dose escalation were included in the PAS
[b] Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later)
CLIA = Clinical Laboratory Improvement Amendments; CS = company submission; IA = Investigator Assessment; IAS = Integrated Analysis Set; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; PAS = Primary Analysis Set; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; RET = rearranged during transfection; SAS = Supplemental Analysis Set; SAS1 = Supplemental Analysis Set 1; SAS2 = Supplemental Analysis Set 2; SAS3 = Supplemental Analysis Set 3; SCE = Summary of Clinical Efficacy; US = United States

An interim analysis was conducted for 796 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 15 June 2021 data cut-off.[29] Unless noted otherwise, the results presented and analysed in this submission are based on this data cut-off. The safety evaluable data set includes all 796 patients treated with selpercatinib as of the 15 June 2021 data cut-off.

Table 3.10: Statistical methods for the primary analysis of LIBRETTO-001

Trial name	LIBRETTO-001
Hypothesis objective	**Phase I:** The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib. **Phase II:** The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	Efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyses. The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the Investigator are presented in Appendix L.[8] For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response. BOR was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e., the crude proportion of patients with best overall response of CR or PR) . Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions. The estimate of the ORR was accompanied by 2-sided 95% exact binomial CIs. To assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analyses were performed. These analyses were conducted in all the analysis sets including the SAS1 population.
Sample size, power calculation	**Phase I** The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1 to 8), a total of approximately 120 patients would be enrolled in Phase I. **Phase II** For Cohort 2, the population of relevance for this submission, (patients with *RET* fusion-positive solid tumours without prior standard first line therapy), a true ORR of ≥55% was hypothesised when selpercatinib was administered to such patients. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35%.

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

Based on Table 8, CS[3]

BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RP2D = recommended Phase II dose; RANO = response assessment in neuro-oncology criteria; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

A variety of outcomes were employed to explore the efficacy of selpercatinib in treatment-naïve patients with *RET* fusion-positive NSCLC. Definitions for these outcome measures are presented in Table 3.11.

Table 3.11: Definitions for outcome measures used in LIBRETTO-001

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

Outcome measure	Definition
	functioning or greater symptomology. EORTC QLQ-C30 subscale scores range from 0 to 100. Descriptive analyses reported median/quartile, mean/SD and mean change/standard error from baseline for each subscale at each study visit. A minimal clinically meaningful difference was defined as at least a 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[31] Patients with "improvement" were defined as those who demonstrated a ≥10-point improvement from their baseline score. Patients with "worsening" were defined as those who demonstrated a deterioration by ≥10-points from their baseline score. A sustained change (improvement or worsening) was defined as an improvement or worsening, respectively, (as defined above) without any further change in score ≥10 points.
Based on Table 9, CS[3] BOR = best overall response; CR = complete response; DOR = duration of response; EORTC QLQ = European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease	

3.2.2.2 LIBRETTO-321

Only the analysis pertaining to the eight participants who were treatment naïve, and RET fusion-positive NSCLC is relevant to this report. The ORR was estimated based on the observed proportion of patients whose BOR was confirmed as CR or PR as determined by the IRC and the Investigator. The estimates of the ORR were accompanied by a two-sided 95% exact binomial confidence interval (CI) calculated using the Clopper-Pearson method.

3.2.3 Baseline characteristics

3.2.3.1 LIBRETTO-001

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

The median age of patients with in the SAS1 population was 63 (range: 23–92) years and a greater proportion of participants were female (62.3%; Table 3.12). The majority (69.6%) of patients were white, with a high proportion of patients identified as Asian (18.8%). Most participants (69.6%) reported never smoking. The younger age, as well as the higher proportion of females, Asian patients and non-smokers is reported by the company to be consistent with the patient profile of *RET* fusion-positive NSCLC reported in the literature and mirrors the real-world patient profile in England.

In the SAS1 population, the median time from diagnosis was [redacted] months ([redacted] Most patients (98.6%) had metastatic disease at enrolment, with 23.2% exhibiting CNS metastases at baseline. In addition, most patients were diagnosed with Stage IV or greater disease (91.3%). This was higher than England, where 46.8% of NSCLC patients were diagnosed at Stage IV in 2017. Next generation sequencing (NGS) on tumour samples [redacted] was the most common method of determining *RET* fusion status, which will mirror English clinical practice following the growing establishment of Genomic Hubs (Table 3.13).

In line with the population described in the decision problem, no patients in the SAS1 subgroup had received prior systemic therapy or treatment other than cancer surgery ([redacted]) or radiotherapy ([redacted] Table 3.14).

Table 3.12: Baseline demographic characteristics for treatment-naïve RET fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve), N=69
Age, years	
Median (range)	63.0 (23–92)
Age group, n (%)	
18–44 years	[redacted]
45–64 years	[redacted]
65–74 years	[redacted]
75 –84 years	[redacted]
≥85 years	[redacted]
Sex, n (%)	
Male	26 (37.7)
Female	43 (62.3)
Race, n (%)	
White	48 (69.6)
Black	4 (5.8)
Asian	13 (18.8)
Other/Missing	4 (5.8)
Ethnicity, n (%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Missing	[redacted]
Body weight, kg	
Median (range)	[redacted]
Baseline ECOG, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
Smoking history, n (%)	
Never smoked	48 (69.6)
Former smoker	19 (27.5)
Current smoker	2 (2.9)

Based on Table 10, CS[3]
CS = company submission; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Table 3.13: Baseline disease characteristics for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve), N=69
Stage at diagnosis, n (%)	
I, IA, IB	[redacted]
II, IIA, IIB	[redacted]
IIIA, IIIB	[redacted]
IIIC	[redacted]
IV	[redacted]
IVA	[redacted]
IVB	[redacted]
IVC	[redacted]
Missing	[redacted]
Time from diagnosis, months	
Median (range)	[redacted]
History of metastatic disease, n (%)	
Yes	[redacted]
No	[redacted]
Time from diagnosis of metastatic disease, months	
Median	[redacted]
Range	[redacted]
At least one measurable lesion by investigator, n (%)	
Yes	[redacted]
No	[redacted]
Sum of diameters at baseline by investigator, mm	
Median (range)	[redacted]
CNS metastases at baseline by investigator, n (%)	
Yes	16 (23.2)
No	53 (76.8)
***RET* fusion partner, n (%)**	
KIF5B	48 (69.6)
CCDC6	10 (14.5)
NCOA4	1 (1.4)
Other	[redacted]
Unknown	[redacted]
Molecular assay type, n (%)	
NGS on tumour	[redacted]
PCR on tumour	[redacted]
NGS on plasma/blood	[redacted]
FISH on tumour	[redacted]

Characteristics	SAS1 (treatment-naïve), N=69
Nano string technology	[redacted]
Based on Table 11, CS[3] CNS = central nervous system; CS = company submission; FISH = fluorescent in situ hybridisation; NGS = next generation sequencing; NSCLC = non-small-cell lung cancer; PCR = polymerase chain reaction; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

Table 3.14: Prior cancer-related treatments for *RET* fusion-positive NSCLC

Characteristics	SAS1 (treatment-naïve), N=69
Prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior radiotherapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior cancer related surgery, n (%)	
Yes	[redacted]
No	[redacted]
Based on Table 12, CS[3] CS = company submission; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

The patient disposition of the SAS1 analysis set is presented in Table 3.15. Of the 69 patients included, [redacted] were still on treatment as of the 15 June 2021 data cut-off. For all patients, the most common reason for treatment discontinuation was [redacted].

Table 3.15: Patient disposition of *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (15 June 2021 data cut-off)

Characteristics	SAS1 (treatment-naïve), N=69
Treated	**69**
Treatment ongoing, n (%)	**32 (46.4)**
Treatment discontinued, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]
Other	[redacted]
Treatment continued post-progression, n (%)	[redacted]
Study status:	
Continuing study, n (%)	[redacted]
Discontinued study, n (%)	[redacted]
Reason for study discontinuation	
Withdrawal of consent	[redacted]
Death	[redacted]

Characteristics	SAS1 (treatment-naïve), N=69
Based on Table 13, CS[3] CS = company submission; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

EAG comment: Outcomes are presented and used in all analyses (ITC and CEA) for the SAS1 population of LIBRETTO, but it is unclear if the SAS1 population includes all eligible participants. The company was asked to confirm that the patients in the SAS1 are all the RET fusion-positive NSCLC patients that were included in LIBRETTO-001 and that there were no RET fusion-positive NSCLC patients treated in LIBRETTO-001 omitted from the SAS1. The company responded by stating that, *"Lilly can confirm that all treatment-naïve RET-fusion positive NSCLC patients enrolled into the LIBRETTO-001 trial were included in the SAS1 population"*.[13] The EAG appreciates this clarification.

3.2.3.2 LIBRETTO-321

Baseline characteristics for the eight participants who were treatment naïve are not presented in the paper. For the 26 who were RET fusion-positive NSCLC (but 18 of whom were *not* treatment naïve), the median age was 52, median weight was 60.6 kg, 88.5% had an ECOG of 1, and 19 had never smoked.

3.2.4 Subsequent therapy

No information on subsequent therapy was provided in the CS.[3]

EAG comment: The company was asked to provide the distribution of subsequent therapy in LIBRETTO-001, which they provided (see Table 3.16).[13] However, the EAG have found it difficult to reconcile these numbers to each other. The company were also asked to provide a comparison of these figures with NHS clinical practice and to discuss the implications of any discrepancies. In response, the company reproduced Table 61 from the CS as Table 8 in the clarification letter response.[3, 13] This is based on clinical expert opinion, which the EAG acknowledges might be necessary in the absence of experience of selpercatinib for this indication in the NHS. However, as the company point out, there is a large discrepancy between Table 61 and Table 3.16: Table 61 shows that clinical experts believe the following distribution (%) applies to clinical practice:

- Docetaxel 0
- Docetaxel plus nintedanib 0
- Nivolumab 0
- Pembrolizumab plus pemetrexed plus platinum chemotherapy 5
- Atezolizumab/pembrolizumab 5
- Pemetrexed plus platinum chemotherapy 70
- Best supportive care 20

However, notwithstanding the difficulty in reconciliation, in the LIBRETTO-001 it appears that very few patients received pemetrexed plus platinum chemotherapy and none received something that might be regarded as best supportive care. In contrast, it seems that about [redacted] received pembrolizumab in some combination. If there is a mismatch between the trial and NHS clinical practice, this could lead to two potential biases i.e., in effectiveness if a higher proportion of more effective immunotherapy combination treatments were administered in the trial, and in cost if the economic model assumed the lower proportion of those treatments. The potential mismatch in subsequent therapy distribution between LIBRETTO-001 and clinical practice therefore constitutes a key issue.

Table 3.16: Summary of subsequent therapies of patients in the LIBRETTO-001 trial

Type of anti-cancer therapy	SAS1 patients ([redacted]), n (%)	SAS1 patients who received subsequent therapy ([redacted]), %
Chemotherapy	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
TS-1	[redacted]	[redacted]
Avastin (bevacizumab)	[redacted]	[redacted]
Carboplatin/pembrolizumab	[redacted]	[redacted]
Carboplatin/pemetrexed/bevacizumab	[redacted]	[redacted]
Carboplatin, pemetrexed, pembrolizumab	[redacted]	[redacted]
Carboplatin, pemetrexed, and pembrolizumab	[redacted]	[redacted]
Carboplatin/pemetrexed/pembrolizumab	[redacted]	[redacted]
Maintenance pemetrexed and pembrolizumab	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed (Alimta)	[redacted]	[redacted]
Pemetrexed/pembrolizumab	[redacted]	[redacted]
Targeted therapies	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]
BLU-667	[redacted]	[redacted]
ADC68, PDNA, tremelimumab and PF-06801591	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Pembrolizumab (Keytruda®)	[redacted]	[redacted]
Radiation to the right lung 5000CGY ended on 15 January 2020	[redacted]	[redacted]
Other	[redacted]	[redacted]
Avastin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]

Based on Table 32, clarification letter response[13]
SAS1 = Supplemental Analysis Set 1

3.2.5 Risk of bias assessment

3.2.5.1 LIBRETTO-001

The LIBRETTO-001 trial was assessed for risk of bias and generalisability in line with NICE requirements. Overall, the results of the LIBRETTO-001 trial may be considered at low risk of bias, as summarised in Table 3.17.

Whilst LIBRETTO-001 was single arm in nature, the trial was reported by the company as having:

- a clearly focussed issue,
- accurately measured exposure and outcome to minimise bias, and
- results which were considered by the company to be precise, believable and generalisable to the UK population.

Table 3.17: Quality assessment of the LIBRETTO-001 trial

Study Question	Grade (Yes/No/Unclear)
1. Did the study address a clearly focussed issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib in patients with advanced solid tumours including *RET* fusion-positive solid tumours. The primary endpoint of Phase I was MTD and/or the RP2D of selpercatinib. The primary endpoint of Phase II was ORR and secondary endpoints include DOR, PFS and OS.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined in Drilon et al. 2020b[32]. However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes. This was a prospective study with an appropriate study design with validated tools for outcome assessment and data collection. All patients were classified using the same criteria.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1 and assessed by an IRC. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No. Confounding factors were not listed; however, baseline characteristics are extensively reported.
5B. Have they taken account of the confounding factors in the design and/or analysis?	The study has no control arm; therefore, randomisation or stratification are not applicable.
6A. Was the follow up of subjects complete enough?	Yes. Out of the 69 subjects enrolled in the treatment-naïve cohort of LIBRETTO-001, a high proportion of patients (46.4%) were continuing treatment at the latest data cut-off.[29]
6B. Was the follow up of subjects long enough?	The follow-up of subjects was long enough to collect a sufficient number of PFS events and estimate the median, however the median OS was not estimable due to a low proportion of events.
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked anti-tumour activity in treatment-naïve *RET* fusion-positive NSCLC patients, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with RECIST assessment used on all scans to determine the ORR with an IRC. Response was confirmed by a repeat assessment no less than 28 days later.
9. Do you believe the results?	Yes. The primary endpoint for Phase II (ORR) aligns with published results from trials for other *RET* selective inhibitors.[33]

Study Question	Grade (Yes/No/Unclear)
10. Can the results be applied to the local population?	Yes. These results can be applied to treatment-naïve patients with *RET* fusion-positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.[33] ORR was 70% in treatment-naïve NSCLC patients treated with pralsetinib in a Phase 1/2 trial compared to 84.1% in the LIBRETTO-001.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first- and subsequent lines of therapy.
Based on Table 14, CS[3] CS = company submission; CTCAE = common terminology criteria for adverse events; DOR = duration of response; IRC = Independent Review Committee; MTD = maximum-tolerated dose; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection; RP2D = recommended phase 2 dose	

EAG comment:

- The CASP appraisal checklist for cohort studies has been used. Questions 5A and 5B have not been answered satisfactorily. Evading the issue of confounding because of the lack of a comparator arm demonstrates a lack of understanding of confounding. Confounding – where outcomes are affected by variables other than the independent variable – does not only result from a mismatched comparator and will also occur in a single arm trial as a result of uncontrolled threats to internal validity, such as the placebo effect or history effects. These issues should have been mentioned in the comments. Therefore, the major flaw of this single arm trial – that it was not possible to extricate treatment effects from intervening effects because of the lack of a control arm – was not highlighted. The lack of appreciation of this is suggested by the company's comment for Question 7, where all of the improvement in outcomes in the single arm is uncritically attributed to a treatment effect, even though a complete absence of any contributary effect from intervening variables upon outcomes is extremely unlikely.
- Question 8 appears to have been misunderstood, with no comment on the precision of the estimates (for example, there should have been a comment on the spread of the 95% CIs relative to the null line).

3.2.5.2 LIBRETTO-321

The EAG used the CASP evaluation tool to assess the quality of the LIBRETTO-321 trial.[24]

Table 3.18: Quality assessment of the LIBRETTO-321 trial

Study Question	Grade (Yes/No/Unclear)
1. Did the study address a clearly focussed issue?	Yes.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes.

Study Question	Grade (Yes/No/Unclear)
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No.
5B. Have they taken account of the confounding factors in the design and/or analysis?	No.
6A. Was the follow up of subjects complete enough?	Yes.
6B. Was the follow up of subjects long enough?	The follow-up of 9.7 months was insufficient for valid measurement of outcomes. In the discussion the authors stated: "*at the time of analysis, many patients remained progression free, and responses were ongoing. Therefore, survival data were not mature, and median PFS and OS could not be estimated*"
7. What are the results of this study?	Selpercatinib had suggestions of marked anti-tumour activity in treatment-naïve *RET* fusion-positive NSCLC patients, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with the 95% CI not crossing null for ORR.
9. Do you believe the results?	Yes. This aligns with results from LIBRETTO-001.
10. Can the results be applied to the local population?	Yes. These results can be applied to treatment-naïve patients with *RET* fusion-positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first- and subsequent lines of therapy.

Based on Lu et al. 2022[24]
CI = confidence interval; CTCAE = common terminology criteria for adverse events; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection

3.2.6 Efficacy results of the included studies

Outcomes have been ordered according to the NICE scope:

- OS
- PFS
- Response rate
- TTD
- Adverse effects of treatment
- HRQoL

EAG comment: The company additionally measured DOR, which has not been included in this report as it is not included in the NICE scope. This issue has been explored in detail in Section 2.4.

3.2.6.1 Overall survival

3.2.6.1.1 LIBRETTO-001

For assessment of OS, the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause) was recorded. Patients who were alive or lost to follow-up as of the data cut-off date were right-censored (see detailed censoring criteria listed in Table 3.10). The censoring date was determined from the date the patient was last known to be alive.

The median OS in the SAS1 trial population was [redacted] at the 15 June 2021 data cut-off, with the majority of patients (49; 71%) remaining alive at a median follow-up of 25.20 months. At 12 months, the OS rate was 92.7% (95% CI: 83.3–96.9) and at 24 months was 69.3% (95% CI: 55.2–79.7), providing preliminary evidence to support that selpercatinib will result in an extension to patients' lives (Table 3.19). The Kaplan-Meier (KM) plot for OS is presented in Figure 3.1.

Table 3.19: OS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

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

Based on Table 18, CS[3]
[a] Status as of the patient's last disease assessment 15 June 2021
[b] Estimated based on Kaplan-Meier method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% CI was calculated using Greenwood's formula
CI = confidence interval; CS = company submission; NSCLC = non-small-cell lung cancer; NE = not estimable; OS = overall survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.1: Kaplan-Meier plot of OS for treatment-naïve RET fusion-positive NSCLC (SAS1)

Based on Figure 8, CS[3]
Censored patients denoted by "+".
CS = company submission; NSCLC = non-small cell lung cancer; OS = overall survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

EAG comment: Evidence from LIBRETTO-001 is based on a 15 June 2021 data cut-off. Median OS was [redacted]. The company has been asked to provide evidence from a later cut-off and let the EAG know when the next data cut-off will be available. The company responded by stating that, "*At this current time, no data from a later data cut-off from the LIBRETTO-001 trial are available. The next data cut-off from the LIBRETTO-001 trial is anticipated to occur in* [redacted]*, with results expected to become available in* [redacted]". The EAG is satisfied with this response.

3.2.6.1.2 LIBRETTO-321

Survival data were not mature, and median OS could not be estimated.

3.2.6.2 Progression-free survival

3.2.6.2.1 LIBRETTO-001

Progression-free survival was derived for each patient as the number of months from the date of the first dose of the study drug until documented disease progression or death due to any cause. Patients were censored as per the criteria listed in Table 3.10.

As of the 15 June 2021 data cut-off, the majority (37; 53.6%) of patients were alive and without documented PD, with a median duration of PFS of 22 months (95% CI: 13.8–NE) months. Death or disease progression was reported in 29/69 (42%) of patients over a median follow-up of 21.9 months. Due to the majority of patients remaining progression-free at the cut-off date, the PFS data are considered immature (Table 3.20). The majority [redacted] of patients were progression-free for ≥12 months, as of the June 2021 data cut-off.

By KM estimates, the probability of patients being progression-free at 6- and 12- months was [redacted] and 70.6% (95% CI: 57.8–80.2), respectively, by Independent Review Committee (IRC) assessment. These results indicate that administration of selpercatinib can produce clinically meaningful responses for a high proportion of treatment-naïve patients, with over two thirds estimated to be event-free (death or disease progression) for at least a year after receiving their first dose. Progressed disease is associated with reduced patient HRQoL, and as such, selpercatinib is likely to bring positive benefits to treatment-naïve *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their QoL for longer periods of time. The KM plot of PFS is presented in Figure 3.2.

Table 3.20: PFS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve), N=69
Progression status n (%)[a]	
Disease progression	29 (42.0)
Died (no disease progression beforehand)	[redacted]
Censored	37 (53.6)
Reason censored (n, %)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without document PD	[redacted]
Discontinued from study without documented PD	[redacted]
Discontinued treatment and lost to follow-up	[redacted]

Criteria	SAS1 (treatment-naïve), N=69
Duration of PFS (months)[b, c]	
Median	22.0
95% CI	[redacted]
Minimum–maximum	[redacted]
Rate (%) of PFS[b,d]	
≥6 months (95% CI)	[redacted]
≥12 months (95% CI)	70.6 (57.8–80.2)
≥24 months (95% CI)	41.6 (26.8–55.8)
≥36 months (95% CI)	[redacted]
Duration of PFS follow-up (months)[b]	
Median	22.0
25th, 75th percentiles	[redacted]
Observed PFS, n (%)	
<6 months	13 (18.8)
≥6 to 12 months	17 (24.6)
≥12 to 18 months	13 (18.8)
≥18 to 24 months	13 (18.8)
≥24 months	13 (18.8)

Based on Table 17, CS[3]
[a] Status as of the patient's last disease assessment 15 June 2021
[b] Estimated based on KM method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% CI was calculated using Greenwood's formula
CI = confidence interval; IRC = Independent Review Committee; KM = Kaplan-Meier; NSCLC = non-small-cell lung cancer; PD = progressive disease; PFS = progression-free survival; NE = not estimable; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.2: Kaplan-Meier plot of PFS based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Based on Figure 7, CS[3]
Censored patients denoted by "+".
CS = company submission; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

3.2.6.2.2 LIBRETTO-321

Survival data were not mature, and median PFS could not be estimated.

3.2.6.3 Response Rate

3.2.6.3.1 LIBRETTO-001

The ORR was defined as the proportion of patients with a BOR of confirmed CR or PR based on RECIST v1.1 (see Table 3.11). In the SAS1 trial population, the ORR was 84.1% (58/69, 95% CI: 73.3–91.8) as per IRC assessment (Table 3.21). Based on BOR, 9% of patients were assessed to have stable disease, whilst the majority were assessed to have a partial response (78.3%). Only three patients (4%) were assessed to have PD as BOR.

The individual patients' responses to selpercatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, are illustrated in Figure 3.3, demonstrating that at the data cut-off, tumour diameter had decreased in all of the 69 patients, decreasing by more than 30% (i.e., at least a partial response was achieved) in all but [redacted] patients. The company concludes that these results indicate that selpercatinib treatment results in high response rates in treatment-naïve *RET* fusion-positive NSCLC patients, delaying disease progression and decreasing tumour size.

Table 3.21: BOR and ORR for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

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

Based on Table 15, CS[3]
BOR = best overall response; CI = confidence interval; CS = company submission; CR = complete response; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PR = partial response; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.3: Waterfall plot of best change in tumour burden based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Based on Figure 5, CS[3]

Footnotes: Dotted lines indicate thresholds for PR and PD. A decrease in tumour size of ≥30% was considered a PR, whilst an increase in tumour size of ≥20% was considered PD.

CS = company submission; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PD = progressive disease; PR = partial response; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

3.2.6.3.2 LIBRETTO-321

The BOR and ORR were evaluated by LIBRETTO-321 [24] (Table 3.22). The ORR was 87.5% (95% CI: 47.3 to 99.7).

Table 3.22: BOR and ORR for treatment-naïve *RET* fusion-positive NSCLC patients

Criteria	N=8
Best overall response, n (%)	
Complete response	1(12.5)
Partial response	6(75.0)
Stable disease	1(12.5)
Progressive disease	0
Not evaluable	0
Objective response rate (CR plus PR)	
n (%)	7 (87.5)
95% CI	(47.3–99.7)

Based on Lu et al 2022.[24]
BOR = best overall response; CI = confidence intervals; CR = complete response; NSCLC = non-small-cell lung cancer; ORR = objective response rate; PR = partial response; RET = rearranged during transfection

3.2.6.4 Time to treatment discontinuation

No data presented by company.

3.2.6.5 Health-related Quality of Life

3.2.6.5.1 LIBRETTO-001

The EORTC QLQ-C30 was used as the treatment-specific quality of life (QoL) measure.

As of the 15 June 2021 data cut-off, [redacted] patients in the SAS1 trial population had completed a baseline assessment as part of a "QLQ-C30 Analysis Set" and at least one following assessment. The EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks during the first year, at visit 13 and then every 12 weeks until the end of treatment (EoT) visit, and then at the follow-up visit after treatment discontinuation (see Table 3.11 for further details of EORTC QLQ-C30 methodology).

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

Across the majority of the QLQ-C30 subscales, a numerically higher proportion of NSCLC patients reported improved scores versus worsening QLQ-C30 subscale scores (Table 3.23). Overall, at the data cut-off the majority of treatment-naïve advanced *RET* fusion-positive NSCLC patients had improved QoL as determined by QLQ-C30 subscales during treatment with selpercatinib.

Table 3.23: EORTC QLQ-C30: Proportion of patients with *RET* fusion-positive NSCLC who improved or worsened from baseline at scheduled follow-up visits

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

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

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

Based on Table 19, CS[3]
Footnotes: Patients who were "improved" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients who "worsened" were defined as those who demonstrated a decrease by ≥10-points from their baseline score
CS = company submission; EORTC QLQ = European Platform of Cancer Research Quality of Life Questionnaire; EoT = end of treatment; NSCLC = non-small-cell lung cancer; QoL = quality of life; RET = rearranged during transfection

3.2.6.5.2 LIBRETTO-321

Health-related quality of life data were not presented.

3.2.7.5 Sub-grouping

3.2.7.5.1 LIBRETTO-001

As described in Table 3.7, to assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analysis based on demographic and baseline characterises was performed on the SAS1 trial population. The ORR remained consistent across the prespecified subgroups, demonstrating the efficacy of selpercatinib to be robust to variations in demographics and baseline characteristics (Figure 3.4 and Figure 3.5).

In addition, owing to the high prevalence of brain metastases in *RET* fusion-positive NSCLC patients the efficacy of selpercatinib in the subset of patients with brain metastases was investigated. A total of 16 (23.2%) of the 69 treatment-naïve patients had Investigator assessed brain metastases at baseline. Five patients had measurable CNS disease by IRC and 11 patients had non-measurable CNS disease by IRC. Figure 3.5 shows the effect on ORR.

The CS also reported that patients with measurable CNS lesions had a CNS ORR of [redacted] demonstrating efficacy of selpercatinib against CNS metastases (Table 3.24).

Figure 3.4: Forest plots for the subgroup analysis on the ORR based on demographic characteristics (SAS1)

Based on Figure 9, CS[3]

Footnote: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.

CI = confidence interval; CS =company submission; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.5: Forest plots for the subgroup analysis on the ORR based on baseline disease characteristics (SAS1)

Based on Figure 10, CS[3]

Footnote: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.
CI = confidence interval; CNS = central nervous system; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; NGS = next generation sequencing; ORR = objective response rate; PCR = polymerase chain reaction; PD-1 = programmed cell death 1 receptor; PD-L1 = programmed cell death receptor ligand 1; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Table 3.24: CNS ORR and DOR by IRC assessment - RET fusion-positive treatment-naïve patients with measurable CNS lesions

	NSCLC with prior RT			No prior brain RT (N=3)	All NSCLC (SAS1) (N=5)
	Brain RT ≤2 months prior to first dose (N=2)	Brain RT >2 months prior to first dose (N=0)	All NSCLC with prior RT (N=2)		
CNS ORR[a] (CR plus PR)					
Number of Patients with CR plus PR (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS CBR					
Number of patients with CR plus PR plus SD[c] (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS DOR (months)[d]					
Number of patients censored, n (%)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	N/A	[redacted]	[redacted]	[redacted]

Based on Table 20, CS[3]

[a] CNS ORR is defined as the proportion of patients with best overall response of CR or PR. Response was confirmed by a repeat assessment no less than 28 days

[b] 95% CI was calculated using Clopper-Pearson method

[c] Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met

[d] Estimate based on KM method

[+] Censored observation

CBR = clinical benefit rate; CI =confidence interval; CNS = central nervous system; CR = complete response; CS = company submission; DOR = duration of response; IRC = Independent Review Committee; KM = Kaplan_Meier; N = number of patients; n = number of patients in specific category; N/A = not applicable; NSCLC = non-small-cell lung cancer; ORR = objective response rate; PR = partial response; RET = rearranged during transfection; RT = radiation therapy; SD = standard deviation

EAG comment:

- Subgrouping was planned for the existence of brain metastases. The company was asked to justify the choice of this sub-grouping variable in terms of how the existence of brain metastases are expected to influence the efficacy of selpercatinib. The company responded by stating that, "*A subgroup analysis to assess overall responses rates based on the RECIST 1.1 criteria, assessed by IRC, in patients with Investigator assessed brain metastases was performed in LIBRETTO-001. Differential efficacy of selpercatinib in this subgroup of patients was not anticipated as compared with RET-fusion positive patients without brain metastases, however this subgroup analysis was pre-specified owing to the high prevalence of brain metastases in patients with RET rearrangements, with an estimated lifetime prevalence of 46% in Stage IV disease, and the detrimental impact of brain metastases on survival. A real-world evidence study estimated a significantly shorter life expectancy for NSCLC patients with brain metastases (25.3 weeks) compared with patients with metastases in the contralateral lung (50.5 weeks), bone (49.4 weeks), adrenal glands (48.7 weeks) and liver (44.9 weeks) (p<0.01 for all comparisons). Available clinical data for selpercatinib evidences its high efficacy in RET fusion positive patients with brain metastases: the Summary of Product Characteristics (SmPC) for selpercatinib states that in 23 RET fusion-positive NSCLC patients with measurable CNS lesions in the LIBRETTO-001 trial, the overall response rate (ORR) in the evaluable patients was 87%.19 These data are supported by the subgroup analysis performed in the SAS1 (treatment-naïve NSCLC) trial population of the LIBRETTO-001 trial which found that patients with measurable CNS lesions had a CNS ORR of* [redacted]." This response appears to imply that the aim of the sub-group analysis was to demonstrate that despite the worse prognosis for people with brain metastases, the efficacy of selpercatinib is independent of the existence of brain metastases. The point estimates in Figure 3.5 do not appear to support the notion that the efficacy of selpercatinib is independent of the existence of brain metastases, as a clear difference in ORR point estimates exists between the sub-groups. Although there is probably some uncertainty, the analysis was almost certainly underpowered to detect a significant difference in effect between the sub-groups, and so the prudent response to this would be to state that a type II error may be responsible for the 'lack of significance', and that a true sub-group difference *may* exist (even if undetected as a statistically significant effect). The company's conclusion that selpercatinib efficacy is unaffected by the existence of brain metastases is therefore not supported by the evidence. The EAG therefore deem brain metastases to be a potential treatment effect modifier (see Section 3.4.1.5 regarding covariates in the ITC).
- Subgrouping was also planned for 'race'. In the baseline characteristics table in the CS[3] (Table 10) four categories are provided: White, Black, Asian and Other. However in the subgroup analyses in Figure 9 of the CS[3] only three categories are used: White, Asian and Other. Notwithstanding the expected small numbers (that are observed in other subgroup analyses), the company was asked to redo the sub-group analysis for 'race' using all four categories. The company stated that, "*In the SAS1 population of patients in the LIBRETTO-001 trial, there were only 4 patients recorded as 'Black or African American' patients, 4 recorded as 'Other' and 13 recorded as 'Asian'. Therefore, performing subgroup analyses based on these patient numbers would introduce substantial imprecision and potentially bias given that in a subgroup of 4 patients, the estimates might be very far from the subgroup population average. This would occur even if Lilly were to combine the 'Black or African American' subgroup into the 'Other' subgroup; the resulting population size of 8 would still be too small to provide robust and reliable subgroup results. Given that Lilly do not want to exclude these patients from the analysis or combine them with the 'Asian' subgroup, given the known differences for Asian ethnicity, subgroup analyses will not be carried out using all four categories*". The EAG is disappointed that sub-grouping could not be carried out as requested. The

problems arising from the small groups are fully understood by the EAG, and these would have been fully taken into account when interpreting the sub-grouped data. The EAG regards the incomplete sub-group analysis for 'race' to prohibit the assumption that race is not an outcome modifier. However, the EAG notes that the results that are available from the incomplete sub-group analysis suggest that race is not a treatment effect modifier and that results from a full subgroup analysis may not improve clarity on this matter given they would be subject to significant uncertainty owing to the low patient numbers available.

Table 3.25. Ethnicity of patients with *RET* fusion-positive NSCLC lung cancer in LIBRETTO-001

Race, n (%)	SAS1 population (N=69)
White	[redacted]
Black or African American	[redacted]
American Indian or Alaska Native	[redacted]
American Indian or Other Pacific Islander	[redacted]
Asian	[redacted]
Other	[redacted]
Missing	[redacted]

Based on Table 6, Company response to clarification letter.[13]
SAS1 = Supplemental Analysis Set 1

- Any discrepancies between the characteristics of the trial sample and the UK target population may have an impact on the applicability of the trial, provided that discrepant variables are potential outcome modifiers. Given that age, sex, race, ECOG, metastatic disease and CNS metastasis have been identified by the company as potential outcome modifiers (by virtue of being used in pre-planned sub-groups) the company was asked to provide data for the UK target population for each of these variables (using the categories employed in the baseline characteristics tables (CS,[3] Tables 10 and 11)). The company responded by stating that, "*RET fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting RET-fusion. Therefore, there is a lack of data specific to this population of patients in the UK. Despite this, a Lilly-commissioned survey provided some real-world insights on the characteristics of NSCLC patients from 9 countries, including the UK. Characteristics of the 74 UK patients with treatment-naïve RET fusion-positive advanced NSCLC included in the survey are presented in* [Adelphi DSP survey, Table 3.26]. *Due to the rarity of the disease, data for patients with metastatic disease and CNS metastasis specific to the UK are not available. The characteristics of patients in the survey are broadly aligned with the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial: median age (64.7 versus* [redacted] *years, respectively) and the proportion of patients who were not Hispanic or Latino (99% versus* [redacted]*%, respectively) were similar. In addition, the majority of patients (70%) in the survey were found to have an ECOG score of 1, which aligned with the patient characteristics reported in LIBRETTO-001 (58.0%). However, the proportion of males with treatment-naïve advanced NSCLC in the real-world data was higher than reported in LIBRETTO-001 (54% versus 37.7%)*" The EAG appreciates the data provided by the company on the 74 UK participants with treatment-naïve RET fusion-positive advanced NSCLC in the Adelphi DSP survey. The data showed similarities between the UK sample and the SAS1 trial dataset in age, with some differences in sex, ECOG score and molecular assay type. Although the data on ethnicity were similar between the UK sample and the SAS1 trial dataset, these data did not

differentiate between important ethnic groups in the UK. No data were provided for UK patients on history of metastatic disease.

- Meanwhile, the sub-group analyses demonstrated that any metastatic disease, CNS metastases, and age may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier. Whilst it is true that none of the results of the subgroup analysis were found to be statistically significant, a lack of statistical significance is not particularly informative in analyses that were not sufficiently powered, and the EAG believes that the point estimate differences are of sufficient magnitude to imply the possibility of type II errors.
- Therefore, the possibility that any metastatic disease, CNS metastases and race may differ between trial and target population (in the absence of adequate information) and the evidence that CNS metastases and race are possible effect modifiers make it possible that the effects in the trial may not be applicable to those that might be observed in the target population. This has therefore been designated as a key issue, although this is probably not resolvable due to lack of information.

Table 3.26. Characteristics of patients with treatment-naive advanced NSCLC from Adelphi DSP real-world evidence insights and LIBRETTO-001 trial

Characteristics	NSCLC DSP Wave IV, N=74	SAS1 (LIBRETTO-001). N=69
Age, years		
Median	64.7	63.0
Sex, n (%)		
Male	39 (53)	26 (37.7)
Female	35 (47)	43 (62.3)
Race/ethnicity, n (%)		
Hispanic/Latino	1 (1)	[redacted]
Not Hispanic or Latino	73 (99)	[redacted]
Missing	0 (0)	[redacted]
ECOG score at advanced diagnosis, n (%)		
0	11 (15)	25 (36.2)
1	52 (70)	40 (58.0)
2	7 (9)	4 (5.8)
3	1 (1)	0 (0.0)
4	3 (4)	0 (0.0)
Current disease stage, n (%)		
IV or greater	74 (100)	[redacted]
Investigator reported history of metastatic disease, n (%)		
Yes	NR	[redacted]
No	NR	[redacted]
Molecular assay type, n (%)		
NGS with tumour tissue	10 (37)	[redacted]
PCR on tumour	6 (22)	[redacted]
FISH on tumour	15 (56)	[redacted]
NGS on plasma/blood	0 (0)	[redacted]

Nano string technology	0 (0)	[redacted]

Based on Table 7, company response to clarification.[13]
ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridisation; NGS = next generation sequencing; NSCLC = non-small-cell lung cancer; NR = not reported; PCR = polymerase chain reaction; SAS1 = Supplemental Analysis Set 1

- It is pointed out in the CS[3] that 91.3% of those in the SAS1 dataset had stage IV or greater disease, and that this differs from the proportion of patients in England, where the figure is 46.8%. Given this large discrepancy, a sub-group analysis for cancer stage would appear to be appropriate, even though numbers in the group below stage IV will be small. The company was asked to carry out a sub-group analysis for cancer stage. The company responded by stating that, "*Disease stage reported in the LIBRETTO-001 trial is based on initial diagnosis and it is unclear whether data from the English National Cancer Registration database are based on initial diagnosis or based on re-assessment. Therefore, these data may not be generalisable. In addition, the eligibility criteria for the LIBRETTO-001 trial stipulated that patients must have locally advanced or metastatic disease. As patients with advanced disease typically have Stage IIIB disease or higher, the proportion of patients with Stage IV disease in the LIBRETTO-001 trial will inherently be higher and therefore will not be generalise to the proportion of patients with Stage IV disease out of the NSCLC population in England (which includes both early and advanced disease patients). Therefore, due to this analysis group not being generalisable to England NSCLC statistics, a subgroup analysis is not appropriate*." In view of the above response, the EAG agrees that a sub-group analysis for stage might be unnecessary. The NICE scope, and also the company's decision problem, specify 'advanced disease', which might explain the lack of agreement with the English National Cancer Registration figures that are based on all stages of disease.

3.2.7.5.2 LIBRETTO-321

No sub-grouping was undertaken.

3.2.8 Adverse events

3.2.8.1 LIBRETTO-001

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

1. The Overall Safety Analysis Set (OSAS, N=796) includes all patients, regardless of tumour type or treatment history, who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15 June 2021 data cut-off date.
2. The NSCLC Safety Analysis Set (SAS) (N=356) includes all patients with documented RET fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15 June 2021 data cut-off date.

Both safety analysis sets included all 69 treatment-naïve patients with documented RET fusion-positive NSCLC who are the focus of this submission.

3.2.8.1.1 Treatment duration and dosage

Informed by the Phase I dose escalation stage of LIBRETTO-001, the RP2D was 160 mg BID. The range of starting doses and average time on treatment were available for the SAS1 trial population (Table 3.27). Nearly all (66/69 (95.7%)) patients in the SAS1 trial population received the

proposed starting dose of 160 mg BID. The mean time on treatment was 18.27 months with a range between 0.4 and 41.2 months. The relative median dose intensity was similar in the Overall Safety Population (94.46%) and in the RET fusion-positive NSCLC Safety Population (92.71%) (Table 3.28).

Dose reductions were required in [redacted] patients in the OSAS and [redacted] patients in the RET fusion-positive NSCLC SAS, with the most common reason being adverse events (AEs; [redacted] [41%] and [redacted], respectively) (Table 3.29). Dose interruptions occurred in [redacted] of the OSAS and [redacted] of the NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted], respectively). There were [redacted] and [redacted] dose increases in the OSAS and NSCLC SAS, respectively.

Table 3.27: Selpercatinib dosing (SAS1)

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

Based on Table 30, CS[3]
BID = twice daily; CS = company submission; RP2D = recommended Phase II dose; SAS1 = Supplemental Analysis Set 1; SD = standard deviation

Table 3.28: Selpercatinib relative dose intensity (Safety Analysis Sets)

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

Based on Table 31, CS[3]
CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Sets; RET = rearranged during transfection; SAS = Safety Analysis Sets; SD = standard deviation

Table 3.29: Selpercatinib dose modifications (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC; N=356)	OSAS (overall population; N=796)
Dose reduction, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	[redacted] **(41)**

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

[a] Patients started at a lower dose during dose escalation that was subsequently increased
[b] Re-escalation after a dose reduction
AE = adverse event; CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; RET = rearranged during transfection; SAS = Safety Analysis Sets

Adverse events were graded by the Investigator, when applicable, using the NCI CTCAE.

3.2.8.1.2 Treatment-emergent adverse events

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

In the OSAS, 95% of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with 38.6% classed as Grade 3 or Grade 4 (Table 3.30). A similar pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent (3.1%) in the OSAS, with no predominant pattern among the individual AEs reported. One fatal treatment emergent adverse event (TEAE) within 28 days of last dose was attributed to selpercatinib in the OSAS, and zero deaths related to selpercatinib occurred in the NSCLC SAS.

A high proportion of patients in the OSAS (99.9%) experienced at least one TEAE during treatment. The most common TEAEs, defined as occurring in 15% of patients or more, in the OSAS were: oedema (48.5%), diarrhoea (47.0%), fatigue (45.9%), dry mouth (43.2%), hypertension (41%), aspartate aminotransferase (AST) increase (36.7%), alanine transaminase (ALT) increase (35.7%), constipation (32.8%), abdominal pain (33.7%), rash (32.8%) and nausea (31.2%).[29] The vast majority of AEs were classified as Grades 1–2 and deemed to be clinically manageable in clinical practice. Rates of different TEAEs were broadly similar between the OSAS and NSCLC SAS analysis sets, as presented in Table 3.31.

Table 3.30: Summary of safety trends (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC; N=356)	OSAS (overall population; N=796)
Any TEAE, n (%)		
All	356 (100.0)	795 (99.9)
Related to selpercatinib	341 (95.8)	756 (95.0)
Grade 3 or 4 TEAE, n (%)		
All	263 (73.9)	572 (71.9)
Related to selpercatinib	143 (40.2)	307 (38.6)
TEAE leading to treatment discontinuation, n (%)		
All	34 (9.6)	64 (8.0)
Related to selpercatinib	[redacted]	25 (3.1)
TE-SAE, n (%)		
All	[redacted]	353 (44.3)
Related to selpercatinib	[redacted]	87 (10.9)
Fatal TEAE		
All	[redacted]	45 (5.7)
Related to selpercatinib	[redacted]	1 (0.1)

Based on Table 33, CS[3]
CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; RET rearranged during transfection; SAE = serious adverse event; SAS = Safety Analysis Set; TEAE = treatment emergent adverse event

Table 3.31: Common TEAEs of all grades (15% or greater in any Safety Analysis Sets)

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

ALT increased	147 (41.3)	[redacted]	284 (35.7)	91 (11.4)
Abdominal pain	101 (28.4)	5 (1.4)	268 (33.7)	20 (2.5)
Constipation	96 (27.0)	5 (1.4)	261 (32.8)	6 (0.8)
Rash	130 (36.5)	4 (1.1)	261 (32.8)	5 (0.6)
Nausea	112 (31.5)	4 (1.1)	248 (31.2)	9 (1.1)
Blood creatinine increased	92 (25.8)	10 (2.8)	227 (28.5)	15 (1.9)
Headache	94 (26.4)	3 (0.8)	220 (27.6)	11 (1.4)
Cough	87 (24.4)	0 (0.0)	184 (23.1)	0 (0.0)
Dyspnoea	84 (23.6)	16 (4.5)	179 (22.5)	25 (3.1)
Vomiting	78 (21.9)	4 (1.1)	178 (22.4)	14 (1.8)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	168 (21.1)	38 (4.8)
Arthralgia	[redacted]	[redacted]	165 (20.7)	2 (0.3)
Back pain	[redacted]	[redacted]	153 (19.2)	12 (1.5)
Dizziness	[redacted]	[redacted]	152 (19.1)	2 (0.3)
Decrease appetite	[redacted]	[redacted]	150 (18.8)	3 (0.4)
Pyrexia	79 (22.2)	1 (0.3)	135 (17.0)	1 (0.1)
Urinary tract infection	70 (19.7)	8 (2.2)	135 (17.0)	12 (1.5)
Thrombocytopenia	74 (20.8)	20 (5.6)	123 (15.5)	24 (3.0)
Dry skin	[redacted]	[redacted]	122 (15.3)	0 (0.0)
Hypocalcaemia	[redacted]	[redacted]	121 (15.2)	22 (2.8)

Based on Table 34, CS[3]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; AESI = adverse event of special interest; CS = company submission; ECG = electrocardiogram; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; QT = QT interval; RET rearranged during transfection; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event

3.2.8.1.3 Grade 3–4 treatment-emergent adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in 572 (71.9%) patients, irrespective of relatedness to study drug (Table 3.32). The most common Grade 3–4 events were hypertension (19.7%), ALT increase (11.4%), and AST increase (8.8%) in the OSAS. Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion (307 [38.6%]) were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, 263 (73.9%) patients experienced Grade 3–4 TEAEs, irrespective of relatedness to selpercatinib (Table 3.32). A smaller proportion (143 [40.2%]) were considered by the Investigator to be related to selpercatinib. Common TEAEs mirrored the OSAS analysis set.

Table 3.32: Grade 3–4 TEAE (occurring in ≥2% of patients)

Preferred term	SAS (*RET* fusion-positive NSCLC; N = 356)		OSAS (overall population; N=796)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
One or more Grade 3–4 AEs	263 (73.9)	143 (40.2)	572 (71.9)	307 (38.6)
Hypertension	68 (19.1)	49 (13.8)	157 (19.7)	105 (13.2)
ALT increased	53 (14.9)	41 (11.5)	91 (11.4)	72 (9.0)
AST increased	37 (10.4)	24 (6.7)	70 (8.8)	50 (6.3)
Lymphopenia	[redacted]	[redacted]	41 (5.2)	NR
Diarrhoea	15 (4.2)	8 (2.2)	40 (5.0)	16 (2.0)
ECG QT prolonged	21 (5.9)	14 (3.9)	38 (4.8)	27 (3.4)
Pneumonia	[redacted]	[redacted]	34 (4.3)	NR
Fatigue	8 (2.2)	3 (0.8)	25 (3.1)	17 (2.1)
Dyspnoea	16 (4.5)	12 (3.6)	25 (3.1)	14 (2.0)
Thrombocytopenia	20 (5.6)	[redacted]	24 (3.0)	0
Anaemia	[redacted]	[redacted]	23 (2.9)	9 (1.3)
Hypocalcaemia	[redacted]	[redacted]	22 (2.8)	2 (0.3)
Pleural effusion	[redacted]	[redacted]	21 (2.6)	2 (0.3)

Based on Table 35, CS[3]
Grade 3–4 AEs related to selpercatinib are reported if occurring in 15% or more of the populations. Grade 3–4 AEs irrespective of their relationship are reported if occurring in 2% or more of the populations.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; ECG = electrocardiogram; NSCLC = non-small cell lung cancer; NR = not reported; OSAS = Overall Safety Analysis Set; QT = QT interval; RET = rearranged during transfection; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event

3.2.8.1.4. Treatment emergent adverse events of special interest

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

ALT/AST increase

In the OSAS, the TEAE of AST increase was reported in 36.7% patients (28.8% related to selpercatinib; 8.8% Grade 3–4; 6.3% Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in 35.7% of OSAS patients (28.5% related to selpercatinib; 11.5% Grade 3–4; 9.0% Grade 3-4 and related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[29] Although ALT and AST TEAEs were the most common reasons for dose interruptions (ALT = [redacted]%; AST = [redacted]%) and reductions (ALT = [redacted]%; AST = [redacted]%), they led to permanent discontinuation in only [redacted] OSAS patients. In addition, no patients met Hy's Law criteria of drug induced liver injury.

Hypersensitivity

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

In the OSAS, drug hypersensitivity was observed in a [redacted] of patients who had one or more AE of hypersensitivity. The median time to first onset was [redacted] weeks (range: [redacted]). Grade 3 was the worst severity AE for [redacted] patients ([redacted]) and there were no Grade 4 or above hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted] OSAS patients.[29]

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

Hypertension

In the OSAS, the AE of hypertension was reported in 41% of patients (28.1% considered related to selpercatinib), with 19.6% classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension 13.2% were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (141 [39.6%]), with 68 (19.1%) classified as Grade 3 and none as Grade 4.[34] Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. A minority of OSAS patients required dose interruption ([redacted]) and/or reduction ([redacted]). [redacted] patient discontinued therapy due to an AE of hypertension.

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

Notable Event-QT prolongation

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

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

Safety conclusions

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable toxicities across both the NSCLC SAS and OSAS. These toxicities were easily reversable through dose interruption or addressed through dose reduction or concomitant

medication. Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent (8%), meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib. This favourable safety profile is as anticipated given the high specificity of selpercatinib for *RET*.

EAG comment: There are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset). This is a potential problem as it is, as it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue.

3.2.8.2 LIBRETTO-321

Safety was evaluated in all 47 patients with NSCLC. Forty-six (97.9%) had at least one TEAE. Twenty-nine (61.7%) patients had a TEAE of at least Grade 3. The most prevalent TEAEs of at least Grade 3 were increased AST level (21.3%), hypertension (19.1%), increased ALT (17.0%), and thrombocytopenia (17.0%). Treatment emergent adverse events led to discontinuation of the study drug in 3 (6.4%) patients. Two of these - decreased platelet count and abnormal liver function - were deemed related to selpercatinib. The most common TEAEs leading to dose reductions were increased AST (12.8%), hypersensitivity (12.8%), decreased platelet count (8.5%), and increased level of ALT (6.4%). There were no deaths due to TEAEs.

The authors concluded that the data suggest that '*selpercatinib was well tolerated and the safety profile of selpercatinib in Chinese patients with RET altered tumours is consistent with the findings in the global population and East Asians included in LIBRETTO-001.*' [24]

EAG comment: There are no specific AE data for the treatment naïve sub-group (n=8). This is a potential problem as it is it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue.

3.2.8 Ongoing studies

The company stated that additional data from LIBRETTO-001 may become available during the course of the evaluation, based on further data cuts in [redacted].

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

Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN) was mentioned as an international multi-centre real world evidence (RWE) study observing the efficacy and safety of selpercatinib in clinical settings in 50 patients with *RET* fusion-positive NSCLC, 13 of which were treatment-naïve.[35] The company stated that current data are immature (median follow-up of 10 months) but further data collection is planned in the future.

The company stated that if selpercatinib was to receive a recommendation for use on the Cancer Drugs Fund (CDF), data would be collected from LIBRETTO-001, LIBRETTO-431 and SIREN during the course of CDF funding.

EAG comment: Randomised controlled trial data in the population of interest i.e., those who are RET fusion-positive, would be much more useful, and so the company has been asked to provide the earliest

date by which an interim analysis from the randomised LIBRETTO-431 trial might be available, and the outcomes that will be presented. The company responded by stating that, "*The interim analysis will be event driven and will be conducted when approximately* [redacted] *events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in* [redacted]*, with results expected to be available from* [redacted]."[13] In contrast to the unbiased estimate in the correct population expected from this RCT, the current CS relies on an ITC between the single arm study of LIBRETTO-001 and the single arm of another study, KEYNOTE-189, not in the RET fusion-positive population, with statistical adjustment to reduce bias (see Section 3.4). Therefore, the EAG have identified the lack of RCT data in the correct population as a key issue.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In Section D.2 of the appendices, it was reported that a total of 23,180 publications were identified through electronic database searches. An additional 54 publications were identified via other sources, including grey literature and bibliography searches. As also reported in Section B.2.1 of the CS, following de-duplication of results, 15,819 studies were ultimately screened at the title and abstract stage. Full texts (published articles and conference abstracts) of the remaining 887 records were obtained and assessed for eligibility. A total of 724 records that did not meet the PICOS criteria were excluded. In total, 163 publications reporting on 88 unique trials met the inclusion criteria.

According to the CS, as the first line to progression treatment setting more closely matched the submission decision problem than first line treatments, the company only included studies reporting on 'first line to progression' treatments. As also stated in Section B.2.1 of the CS and D.2 of the appendices, out of the 88 originally eligible trials, a total of 66 first line to progression studies were identified and ultimately included in the clinical SLR. The list of those first line to progression treatments that are relevant to the company's decision problem i.e., KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan is presented in Table 3.33.[17, 18, 20]

The company also reported in Section D.3 of the appendices and B.2.8.2 of the CS that, based on the SLR, of the 70 studies reported in 77 peer-reviewed publications and 44 conference abstracts included in the clinical SLR up until the July 2021 update, 58 studies reported on "first-line to progression treatments" that fully met the SLR eligibility criteria. However, in Section 2.8.2 and Section D.3 of the appendices[8] it was stated that only 31 could be connected in the NMA network: 31 reported OS, 29 reported PFS data, and 27 studies reported ORR data. Those 31 studies are shown in Table 3.34 with the three that are relevant to the company's decision problem i.e., KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan in bold and highlighted in green.[17, 18, 20]

Table 3.33: List of the three included studies for SLR of first line to progression clinical trial evidence for selpercatinib and comparators in the decision problem

Study ID	Clinical trial number	Study reference
KEYNOTE-021[a]	NCT02039674	Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The Lancet Oncology* 2016; 17(11).

Study ID	Clinical trial number	Study reference
		http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/983/CN-01289983/frame.html.
KEYNOTE-189[a]	NCT02578680	Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. New England Journal of Medicine 2018;378(22):2078-92.
KEYNOTE-189 – Japan[a]		Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer science. 2021;112(8):3255-65.

Based on Table 26, CS Appendix D[8]
[a] First update (SLR2)
CS = company submission; SLR = systematic literature review

Table 3.34: Summary of studies used to perform the network meta-analysis

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
1	Schuette 2017	65Plus	BEVc + PEMc	ORR, PFS, OS
			BEVc + PEMc + PLATi	
2	Zhou 2015	BEYOND	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
3	Zhou 2021	CameL	CAMRc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
4	Hellmann 2018	CheckMate 227	PEMc + PLATi	ORR, PFS, OS
			IPIc + NIVOc	
5	Paz-Ares 2021	CheckMate 9LA	PEMi + PLATi + IPIc + NIVOc	OS, PFS
			PEMc + PLATi	
6	Koyama 2018	CLEAR	BEVc + PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
7	Doebele 2015	Doebele 2015	PEMc + PLATi + RAMc	ORR, PFS, OS
			PEMc + PLATi	
8	Sezer 2021	EMPOWER-Lung 1	CEM	PFS, OS
			(GEMi or PACi or PEMc) + PLATi	
9	Galetta 2015	ERACLE	PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
			Nab-PACi + PLATi	
10	West 2019	IMPower 130	ATEZ + CARB + PAC ATEZ + (maintenance)	ORR, PFS, OS
			CARB + PAC + (BSC or PEM) (maintenance)	
11		IMPower132	PEMc + PLATi	ORR, PFS, OS

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
	Nishio 2021		ATEZc + PEMc + PLATi	
12	China, Lu 2021	IMPower132	ATEZc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
			ATEZc + BEVc + PACi + PLATi	
13	Socinski 2018	IMPower150	ATEZ + BEV + CARB + PAC ATEZ + (maintenance) + BEV(maintenance)	ORR, PFS, OS
			BEV + CARB + PAC + BEV (maintenance)	
			ATEZ + CARB + PAC + ATEZ (maintenance)	
14	Johnson 2004	Johnson 2004	BEVc + PACi + PLATi	ORR, OS
			PACi + PLATi	
15	Karayama 2016	Karayama 2016	BEVc + PEMc + PLATi	PFS, OS
			BEVi + PEMc + PLATi	
16	**Langer 2016**	**KEYNOTE-021**	**PEMc + PLATi**	**ORR, PFS, OS**
			PEMc + PEMBROc + PLATi	
			PEMBRO	
			(CARB + PEM) or (CIS + PEM) or (CARB + GEM) or (CIS + GEM) or (CARB + PAC) + PEM (maintenance)	
17	**Gandhi 2018**	**KEYNOTE-189**	**PEMc + PEMBROc + PLATi**	**ORR, PFS, OS**
			PEMc + PLATi	
18	Wu 2020	KEYNOTE-042 China	PEMc + PLATi	OS
			PEMBROc	
			PEMc + PLATi	
19	**Horinouchi 2021**	**KEYNOTE-189 Japan**	**PEMc + PLATi**	**ORR, PFS, OS**
			PEMc + PEMBROc + PLATi	
			PEMBROc	
20	Lee 2016	Lee 2016	PEMc + PLATi	ORR, PFS, OS
			PEMc	
21	LIBRETTO-001	LIBRETTO-001	SELc	ORR, PFS, OS
			PEMc + PLATi	
22	Fukuda 2019	LOGIK1201	BEVc + PEMc	ORR, PFS, OS
			PEMc	
23	Spigel 2018	Spigel 2018	BEVc + PEMc	ORR, PFS, OS
			PEMc	
			BEVc + PEMc + PLATi	

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
24	Yang 2020	ORIENT-11	SINTc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
25	Socinski 2012	Socinski 2012	Nab-PACi + PLATi	ORR, PFS, OS
			PACi + PLATi	
26	Niho 2012	Niho 2012	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
27	Patel 2013	PointBreak	BEVc + PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
28	Zinner 2015	PRONOUNCE	PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
29	Lu 2021	RATIONALE 304	PEMc + PLATi	ORR, PFS, OS
30	Sandler 2006	Sandler 2006	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
31	Sugawara 2021	TASUKI-52	BEVc + PACi + PLATi	ORR, PFS, OS
			NIVOc + BEVc + PACi + PLATi	

Based on Table 27, Appendices.[8]
ATEZ = atezolizumab; BEV = bevacizumab; c = continuous; CAMR = camrelizumab; CARB = carboplatin; CIS = cisplatin; ERL = erlotinib; GEF = gefitinib; GEM = gemcitabine; I = induction; ID = identification; IPI = ipilimumab; m = maintenance; nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; ORR = objective response rate; OS = overall survival; PAC = paclitaxel; PCB = placebo; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; PFS = progression-free survival; RAM = ramucirumab

3.3.1 Characteristics of comparator studies included in decision problem

The three studies, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan in bold and highlighted in green, that are relevant to the decision problem were all in non-squamous histology and ECOG performance status 0 or 1 with baseline characteristics shown in Tables 3.35 and 3.36.[17, 18, 20] The baseline characteristics of the other studies in the NMA have not been summarised here given that they were not necessary for the estimation of the treatment effect between selpercatinib and either pemetrexed plus platinum chemotherapy (estimated using the ITC) or pembrolizumab plus pemetrexed plus platinum chemotherapy (see Section 3.4.1 and network diagrams in Section 3.4.2). Note also that Tables 3.35 and 3.36 also contain information on LIBRETTO-001 for comparison. A comparison is also presented of the subset of characteristics (age, sex, ECOG performance status, smoking status, race and stage) in Section 3.4.1, and only with the pemetrexed plus platinum chemotherapy arm of KEYNOTE-189. The company considered that all three of the studies were comparable enough to be included in the NMA, although the company did identify sources of heterogeneity across all 31 studies in the NMA, which prompted a meta-regression (see Section 3.4.2.3).

Table 3.35: Baseline characteristics 1

Trial name, Primary Author, Year	Intervention	N randomised / ITT	Baseline pop.	Mean age (years)	Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
					n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
LIBRETTO-001, SAS1	SEL	69	69	63.0 median	43	62.3	48	69.6	4	5.8	13	18.8	4	5.8	-	-	48	69.6
KEYNOTE-021, Langer 2016	PEMBRO + PEM + CARB + PEM (maintenance)	60/60	60	61.8	38	63	49	82	4	7	5	8	2	3	-	-	25	75
	PEM + CARB + PEM optional (maintenance)	63/63	63	63.2	37	59	58	92	0	0	5	8	0	0	-	-	14	86
KEYNOTE-189, Gandhi 2018	PEM + (CARB or CIS) + PEMBRO	410	410	65.0 median	156	38	-	-	-	-	-	-	-	-	-	-	11.7	88.3
	PEM + (CARB or CIS)	206	206	63.5 median	97	47.1	-	-	-	-	-	[redacted]	-	[redacted]	-	-	12.1	87.9
KEYNOTE-189 - Japan, Horinouchi 2021	PEM + (CARB or CIS) + PEMBRO	25/25	25	-	-	-	-	-	-	-	-	-	-	-	-	-	28	72
	PEM + (CARB or CIS)	15/15	15	-	-	-	-	-	-	-	-	-	-	-	-	-	20	80

Based on Table 32, Appendices and Ghandi;[8, 17] Table 3.12 for LIBRETTO-001
CARB = carboplatin; CIS = cisplatin; ITT = intention to treat; PEM = pemetrexed; PEMBRO = pembrolizumab; SEL = selpercatinib

Table 3.36: Baseline characteristics 2

Trial Name, Primary Author, Year	Intervention	Baseline population	Histology								ECOG/WHO performance status						AJCC stage			
			Non-squamous NSCLC		Adeno-carcinoma		Large cell		Adeno-squamous carcinoma		0		1		2		IIIB		IV	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
LIBRETTO-001, SAS1	SEL	69	69	100	62	89.9	0	0	-	-	25	36.2	40	58.0	4	5.8	3	4.2	50	91.3
KEYNOTE-021, Langer 2016	PEMBRO + PEM + CARB + PEM (maintenance)	60	60	100	58	97	0	0	-	-	24	40	35	58	-	-	1	2	59	98
	PEM + CARB + PEM optional (maintenance)	63	63	100	55	87	1	2	-	-	29	46	34	54	-	-	2	3	60	95
KEYNOTE-189, Gandhi 2018	PEM + (CARB or CIS) + PEMBRO	410	410	100	394	96.1	5	-	-	-	186	45.4	221	53.9	1	0.2	-	-	-	-
	PEM + (CARB or CIS)	206	206	100	198	96.1	2	-	2	-	80	38.8	125	60.7	0	0	-	0.5	-	99.5
KEYNOTE-189 - Japan, Horinouchi 2021	PEM + (CARB or CIS) + PEMBRO	25	-	-	23	92	-	-	-	-	15	60	10	40	-	-	-	-	-	-
	PEM + (CARB or CIS)	15	-	-	14	93	-	-	-	-	9	60	6	40	-	-	-	-	-	-

Based on Table 33, Appendices and Ghandi 2018;[8, 17] Tables 3.12 and 3.13 and Drilon 2020 for LIBRETTO-001[36]
AJCC = American Joint Committee on Cancer; CARB = carboplatin; CIS = cisplatin; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; PEM = pemetrexed; PEMBRO = pembrolizumab; SAS1 = Supplemental Analysis Set 1; SEL = selpercatinib; WHO = World Health Organization

EAG comment:

- There is a mismatch between sections of the appendices and the CS in reported numbers of papers included in the SLR and therefore that were eligible for the NMA. In Section B.2.1 of the CS and D.2 of the appendices[8] (see Table 3.33), 66 first line to progression studies are listed, but in Section B.2.8.2 of the CS[3] and Section D.3 of the appendices 58 first-line to progression studies are mentioned, from which 31 are included in the NMA. The source of the extra eight studies is unclear but it is probably due to the updated search in April 2022 not retrieving any studies that the company thought relevant to the NMA: "*As the April 2022 SLR update did not identify any further studies that would be informative to the NMA relevant to this decision problem, studies up to the July 2021 update were assessed for inclusion in the NMA".* Nevertheless, it remains unclear to the EAG by which criteria these eight studies were deemed uninformative.
- Although not explicitly stated, it appears that all three studies that compared pembrolizumab plus pemetrexed plus platinum chemotherapy to pemetrexed plus platinum chemotherapy were included in the NMA to indirectly estimate the treatment effect of the former versus selpercatinib given that an ITC was used to estimate the treatment effect of the latter versus selpercatinib. This means that any heterogeneity and trial selection for pooling will have implications for the comparison between selpercatinib and the pembrolizumab combination.
- The most obvious source of heterogeneity is that all LIBRETTO-001 patients were RET fusion-positive and RET fusion status is unknown in the three comparator trials: the implications of this are explored further in Section 3.4.1.5, as are those of other baseline characteristics in terms of what might be a treatment effect modifier or prognostic in the context of the ITC. It is also the case that KEYNOTE-189 Japan is as study of only Japanese patients, which also might limit its applicability.

The implications of any heterogeneity are discussed in Section 3.4.2.4.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Indirect treatment comparison

A NMA was performed to compare the efficacy of selpercatinib to other first line treatments relevant to the decision problem for the outcomes of ORR, PFS and OS (see Section 3.4.2). However, LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced RET fusion-positive NSCLC directly to comparators relevant to the decision problem. To connect selpercatinib to the NMA, the company chose to first conduct an ITC between selpercatinib and pemetrexed plus platinum chemotherapy. This entailed the use of IPD from LIBRETTO-001 selpercatinib arm and the pemetrexed plus platinum chemotherapy arm from the KEYNOTE-189 RCT using propensity score matching (PSM) to account for any differences between trial populations. The company referred to this ITC as the "*generation of [a] pseudo-comparator arm*". Results are given in Section 3.4.2.

EAG comment:

- No justification was provided as to why pemetrexed plus platinum chemotherapy was chosen for the ITC, as opposed to any of the other comparators in the NICE scope or the NMA. Therefore, the EAG requested this as well as an ITC for each of the comparators in the scope. The company response to the clarification letter was, "*As explained in Section B.2.8.1 of the Company Submission, an ITC using IPD of ORR, PFS and OS with only pemetrexed and platinum chemotherapy was conducted using data from the KEYNOTE-189 trial given that it was the only trial for which the necessary IPD were available. Furthermore, Lilly only had permission and access from the third-*

party holder to these data from the KEYNOTE-189 trial for this arm of the study, and thus a comparison with pembrolizumab with pemetrexed and platinum chemotherapy, or any other comparator in the network or scope, could not be conducted… As outlined above, performing an ITC using IPD of the outcomes with all other comparators in the scope is not possible given that IPD data for comparators other than pembrolizumab with pemetrexed and platinum chemotherapy from the KEYNOTE-189 trial are not available." The EAG is concerned that the rationale for the choice of comparator is an administrative reason rather than one that would make the use of other comparators inappropriate.

- The PSM was the method of adjustment for confounding employed in the ITC. Although the company referred to NICE Technical Support Document (TSD) 17, no justification was provided for its choice. Therefore, the EAG requested that NICE TSD 17 be referred to in assessing which are the best methods for adjusting for confounding and perform at least one other type of adjustment for confounding. In fact, no details of the ITC were provided and so the company was also asked to state the nature of the treatment effect being estimated, ATE or ATT and to provide a full technical report with completion of the QuEENS checklist as recommended in NICE TSD 17.[37] The company response to the clarification letter was "*In line with the recommendations provided in NICE TSD17, in addition to PSM, other methods of control arm adjustment were explored, included genetic matching, propensity score weighting (PSW) using a generalised boosted model, and PSW using a logistic regression model. Guidance provided in NICE TSD17 informed the adjustment techniques."*[13] The results of the adjustment techniques explored in the company's response to clarification are provided below.

3.4.1.1 Propensity score matching

This was the default method for matching the pseudo-comparator arm to the selpercatinib arm, which generated results presented in the CS. The IPD from both trials was used to adjust for between-trial differences in observed baseline characteristics known to have an impact on prognosis (see Table 3.37 below) and to assess outcomes in a matched population. The programming code used for the matching process was provided in the clarification letter. The results of the PSM process are provided below. Covariate balance is illustrated in Figure 3.6 below.

Table 3.37: Baseline characteristics of KEYNOTE-189 before and after PSM

Characteristic	SELc (N=[redacted])	Before PSM[a]	After PSM[a]
		PEMc + PLATi (N=[redacted])	PEMc + PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[b], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 9, Company response to clarification letter[13]
a The analysis followed greedy matching algorithm
b Race: other includes non-white, non-Asian and unknown
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; PEM = pemetrexed; PEMBRO = pembrolizumab; PSM = propensity score matching; SEL = selpercatinib

Figure 3.6. Standardised differences and variance ratio plot before and after propensity score matching

Based on Figure 1, Company response to clarification letter.[13]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios (HRs) and 95% credible intervals (CrIs) for selpercatinib versus the pseudo-control arm (Table 3.38).

The KM curves for PFS and OS after PSM are presented in Figure 3.7.

Table 3.38. Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSM

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

Based on Table 10, Company response to clarification letter[13]
CrI = credible interval; OS = overall survival; PFS = progression-free survival; PSM = propensity score matching

Figure 3.7: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSM

Based on Figure 2, Company response to clarification letter[13]

Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; SCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PSM = propensity score matching

3.4.1.2 Genetic matching

Genetic matching uses a genetic search algorithm to find a set of weights for each covariate such that optimal balance is achieved after matching. For this analysis, models were conducted using R 3.6.0 for Linux. The programme code was provided in the response to clarification letter.

The results of the genetic matching approach are provided in Table 3.39 below. Covariate balance is illustrated in Figure 3.8.

Table 3.39: **Baseline characteristics of KEYNOTE-189 before and after genetic matching**

Characteristic	SELc (N=[redacted])	Before genetic matching	After genetic matching
		PEMc + PLATi (N=[redacted])	PEMc + PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[a], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 11, Company response to clarification letter[13]
[a] Race: other includes non-white, non-Asian and unknown
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; PEM = pemetrexed; PLAT = platinum chemotherapy; SEL = selpercatinib

Figure 3.8. Standardised differences and variance ratio plot before and after genetic matching

Based on Figure 3, Company response to clarification letter.[13]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the genetic matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.40).

The KM curves for PFS and OS after genetic matching are presented in Figure 3.9.

Table 3.40: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via genetic matching

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

Based on Table 12, Company response to clarification letter[13]
CrI = credible interval; OS = overall survival; PFS = progression-free survival

Figure 3.9: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following genetic matching

Based on Figure 4, Company response to clarification letter[13]
Footnote: Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival; NSCLC = non-small-cell lung cancer; OS = overall survival

3.4.1.3 Propensity score weighting using a generalised boosted model

Propensity score weighting (PSW) using a generalised boosted model was conducted using the "twang" package. The programme code used for the weighting process is provided in the clarification letter.

The results of the PSW using a generalised boosted model adjustment process are provided below. Propensity score weighting by generalised boosted model was implemented with two methods of measuring and summarising balance across pre-treatment variables. These were mean effect size (es.mean) and maximum of Kolmogorov-Smirnov statistic (ks.max). They resulted in almost identical balancing results (Table 3.41). However, it should be highlighted that the effective sample size in the resultant pseudo-control arm (PEMc plus PLATi) was smaller than when a matching technique was utilised, making the comparison between arms less powerful.

Table 3.41: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after PSW using generalised boosted model

Characteristic	SELc (N=[redacted])	Before PSW	After PSW[a]	
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=50[b]	PEMc + PLATi N_{eff}=50[c]
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before PSW	After PSW[a]	
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=50[b]	PEMc + PLATi N_{eff}=50[c]
Stage III, %	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 13, Company response to clarification letter[13]
[a] The control arm created by propensity score weighting with generalised boosted model algorithm using two methods of measuring and summarising balance across pre-treatment variables; [b] mean effect size (es.mean); [c] maximum of Kolmogorov-Smirnov statistic (ks.max)
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; N = sample size; N_{eff} = effective sample size; PEM = pemetrexed; PLAT = platinum chemotherapy; PSW = propensity score weighting; SEL = selpercatinib

Figure 3.10. Standardised differences and variance ratio plot before and after PSW using generalised boosted model

Based on Figure 5, Company response to clarification letter[13]
es.mean = mean effect size; ks.mean = maximum of Kolmogorov-Smirnov statistic; PSW = propensity score weighting

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.42).

The KM curves for PFS and OS after PSW by generalised boosted model are provided in Figure 3.11.

Table 3.42: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using generalised boosted model

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

Endpoint	Hazard ratio (95% CI)	P-value
Based on Table 14, Company response to clarification letter[13] CI = confidence interval; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting		

Figure 3.11: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using generalised booster model

Based on Figure 6, Company response to clarification letter[13]
Footnote: Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; PSW = propensity score weighing; OS = overall survival

3.4.1.4 PSW using a logistic regression

Propensity score weighting using a logistic regression model was conducted using the "arm" package which utilises the nearest neighbourhood matching procedure. The programme code used for the weighting process was provided in the clarification letter response.[13]

A comparison of baseline characteristics before and after PSW using logistic regression is presented in Table 3.43. After applying PSW using logistic regression, baseline characteristics were between the selpercatinib and pemetrexed plus platinum chemotherapy arms were closer aligned (Figure 3.12). Similar to PSW when using a generalised boosted model, the effective sample size in the resultant pseudo-control arm (PEMc plus PLATi) was smaller than when PSM was utilised, making the comparison between arms less powerful.

Table 3.43: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after PSW using logistic regression

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=31
Age (mean, years)	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=31
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 15, Company response to clarification letter[13]
[a] The analysis followed greedy match as a matching algorithm
c =continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; N = sample size; N_{eff} = effective sample size; PEM = pemetrexed; PLAT = platinum chemotherapy; PSW = propensity score weighting; SEL = selpercatinib

Figure 3.12. Standardised differences and variance ratio plot before and after PSW using logistic regression

[redacted]

Based on Figure 7, Company response to clarification letter[13]
PSW = propensity score weighting

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.44).

The KM curves for PFS and OS after reweighting by PSW using logistic regression are presented in Figure 3.13.

Table 3.44: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using logistic regression

Endpoint	Hazard ratio (95% CI)	P-value
PFS	[redacted]	[redacted]

Endpoint	Hazard ratio (95% CI)	P-value
OS	[redacted]	[redacted]

Based on Table 16, Company response to clarification letter.[13]
CI = confidence interval; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting

Figure 3.13. PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using logistic regression

[redacted]

Based on Figure 8, Company response to clarification letter[13]
NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting

3.4.1.5 ITC Conclusion

The company stated that: "*A clear preference for the selection of an adjustment technique could not be made based on balanced patient characteristics and available estimates alone. PSM was ultimately selected for the adjustment process as the results were associated with the highest external validity; the modelled median PFS and OS were most closely aligned to those observed in KEYNOTE-189 trial for the pemetrexed plus platinum chemotherapy arm. In addition, utilisation of a PSM approach resulted in the most conservative estimates of treatment effect: the PSM approach resulted in the highest median PFS and OS estimates for the pemetrexed plus platinum chemotherapy* arm [see Table 3.43]. *This result is externally valid since, as outlined in response to question B.17a) below, patients in the SAS1 population of the LIBRETTO-001 trial were typically younger and healthier than the advanced NSCLC more generally. As a result, the mean age and number of non-smokers for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were anticipated to be artificially reduced in the adjustment process, thus resulting in increased mPFS and mOS for this population."*[13]

Table 3.45: Comparison of the modelled landmark survival estimates, mPFS and mOS generated via the different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	Month 6	Month 12	Month 18	mPFS (months)	Month 6	Month 12	Month 18	mOS (months)
PSM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adjustment method	Month 6	Month 12	Month 18	mPFS (months)	Month 6	Month 12	Month 18	mOS (months)
PSW using generalised booster model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KEYNOTE-189 (observed)	-	-	-	4.9				10.6

Based on Table 17, Company response to clarification letter[13]
mPFS = median PFS; mOS = median OS; PSM = propensity score matching; PSW = propensity score weighting

EAG comment: KEYNOTE-189 was used as the source of data for the ITC, although no justification for its choice, as opposed to any other trial, was provided in the CS.[3, 17] Also, the populations were sufficiently different to make sufficient overlap impossible for some variables (e.g., those who "never smoked" comprised [redacted] of the selpercatinib cohort but only [redacted] of the propensity-score-matched pemetrexed plus platinum chemotherapy plus placebo cohort). The company were therefore asked to justify its choice and, if it is not demonstrated to be unequivocally better than those, then to perform an ITC using each of those other data sources using either and individual patient data method according to the NICE TSD 17 or a population adjustment method according to NICE TSD 18. The company response to this request in the clarification letter was, "*..., as noted in the response Question A.21) above, the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial was the only arm with available IPD. For this reason, it was utilised to inform the comparator arm. An IPD method was chosen over a population adjusted method, such as a matching-adjusted indirect comparison (MAIC) described in NICE DSU 18, because the insufficient data on outcomes would mean that the latter would create greater bias and cause methodological difficulties. In addition, a MAIC would adjust for population 'moments' only, whereas utilisation of an IPD adjustment method allows patients to be matched based on individual baseline characteristics. Owing to the large imbalances in certain baseline characteristics caused by RET fusion positive NSCLC patients typically being a younger and healthier demographic than typical lung cancer patients, the use of a population adjusted method would greatly reduce the size of the LIBRETTO-001 dataset (n=69). This would lead to increased uncertainty in the results of the ITC. Additionally, this imbalance of key prognostic factors, such as the low percentages of female and Asian patients, is notable in other pemetrexed plus platinum-based chemotherapy trials identified in the NMA, as presented in Table 18* [in clarification letter response]. *Using summary data would have introduced the additional issue of missing baseline data that may not be reported from publications, such as data that included patients who had never smoked. In addition, there were no other trials which reported any data on patients with specifically RET fusion-positive NSCLC. For these reasons, use of a population adjusted approach was not considered appropriate, and as such, alternative ITC approaches were not conducted*."[13] The EAG consider that, in accordance with NICE TSD 17 and NICE TSD 18, an approach that uses IPD to adjust for confounding is ceteris paribus superior to a method that uses population adjustment.[37, 38] It is also useful that the only trial, KEYNOTE-189, to which the company had access, included a comparison with the only other comparator in the decision problem. As discussed in Section 3.1.2, it might also be that this is one of only three trials that included pemetrexed as recommended in the NG122 and as it would be administered in NHS clinical practice i.e., at induction and maintenance, which the company describe as 'treat to progression'. Another one of the three included trials that could have been considered for the ITC is KEYNOTE-021,

which seems to have baseline characteristics that might be similar those of KEYNOTE-189 (See Section 3.3.1)[17, 20] although the necessary IPD data did not seem to have been available from any of the other included studies. However, as stated in Section 2.3, the EAG is not convinced that these should be the only comparators, which might mean that an ITC versus one of the other comparators in the scope might have been appropriate. Choice of trial data for the ITC therefore is a key issue.

In addition to the 142 patients excluded from the KEYNOTE-189 cohort, five patients were removed from the SAS1 dataset (n=69) to facilitate propensity matching. The reasons were ECOG performance status = 2 ([redacted]) and missing stage data ([redacted]). Removal of participants is a necessary part of propensity-matching. However, in this case it appears that 4/5 excluded from the SAS1 dataset were those with the poorest ECOG score, which could lead to a spurious benefit to be observed for the study drug. The company were asked to state whether the decisions on exclusions in the SAS1 database were made pre-hoc. If so, the company were asked to explain the decision-making process underlying the pre-hoc exclusion strategy. The company responded by stating that, *"Lilly can confirm that the decision on patient eligibility was made pre-hoc before the matching/weighting approaches were attempted. The reason for this pre-hoc decision on exclusion from the SAS1 database being made was that the KEYNOTE-189 study had an inclusion criterion to enrol only patients with an ECOG performance score of 0 or 1. Therefore, it would not be possible to find patients from the KEYNOTE-189 trial who matched the [redacted] patients with an ECOG score of 2 in the SAS-1 population of the LIBRETTO-001 trial.*"[13] The EAG are satisfied with this response.

The EAG opinion is that PSM (the default method used in the base-case) does appear to provide the most conservative results for OS and PFS, out of the methods that were explored. However, it is possible that other methods of adjusting for confounding, not explored by the company, may have generated evidence that would have provided even more conservative results than were produced by PSM (the base-case method). Ultimately, the most appropriate method is the one producing the best reduction in bias, which, assuming selection on observables, is the one that produces the best balance of baseline characteristics. All methods explored produced some discrepancies between the arms. *Propensity score matching* led to large between-arm differences for 'never smoked' and both race variables, *genetic matching* led to some between-arm differences for ECOG and 'race other', while *PSW – generalised boosted* led to differences for female and 'race other', and *PSW – logistic regression* led to differences for female, 'never smoked' and 'race'. Overall, it is difficult to judge which of these methods is the best on that basis. However, it is still possible that other methods (that were not explored) may have been able to demonstrate superior balance to these methods. One possibility suggested in NICE TSD 17 if balance is still not good after matching is the addition of multivariate regression on the matched sample.[37] If so, the results from such an unexplored method may have been preferable. Such a preferable method might produce results that demonstrate less of a benefit for selpercatinib than observed in the base-case, implying that the base-case results may be over-estimating the benefits of selpercatinib.

It was also unclear how covariates/baseline characteristics were selected as potential treatment effect modifiers or prognostic. The EAG requested a full description of the method and the company responded by providing the results of a separate SLR in Appendix C of the clarification letter response in the form of a large table that listed the studies that found any one of a number of variables to be prognostic and in which direction.[13] Unfortunately, there was no evidence presented as to how this large table was used to identify the final list of six variables (age, sex, race, smoking status, ECOG performance status, disease stage). Notable omissions of potential prognostic factors were lower weight (all studies showed associated with worse prognosis) and prior therapy (many studies, but complex relationship). Brain metastases were also associated with worse prognosis, having been identified as prognostic in the CS,[3] and having potential for treatment effect modification as revealed

by subgroup analysis of LIBRETTO-001 (see Section 3.2.6). Although the sub-group differences were non-significant, statistical significance/ non-significance is not informative in an analysis that is not sufficiently powered, and the EAG believes, in view of the large differences in point-estimates that there is a possibility of a type II error. Non-squamous histology seemed to confer better prognosis, but studies were selected on that basis anyway. No mention was made of RET fusion status, and this might be because the company had already determined that it was not prognostic: *"Adjustments relating to the presence of RET fusion were not made, due to the inconclusive prognostic nature of a RET fusion, as described in Section B.1.2.1."* (page 72).[3] The EAG notes that Section B.1.2.1 does contain a discussion of the evidence on the prognostic nature of RET fusion status, which suggests that RET fusion-positive is associated with better prognosis. However, it also seems to be associated with characteristics that might confer better prognosis such as younger age, non-smoking status, and better ECOG performance status, as shown in one observational study.[39] The company cited that study's conclusion that any advantage in OS, which had been statistically significant, no longer was after adjusting for baseline characteristics (age, sex, race, practice type (academic or community), body weight, body mass index (BMI), stage at initial diagnosis, tumour histology, smoking status, microsatellite instability (MSI) status, genomic alterations, ECOG performance status, PD-L1 expression (positive = >1% staining versus negative), initial treatment regimen (checkpoint inhibitor use yes/no), and reported metastatic sites). However, the EAG notes that the HR point estimate still favoured RET fusion-positive and that the 95% CI only just crossed 1 (1.52 (0.95, 2.43), p = 0.08), which might be due to the very small number of RET fusion-positive patients (n=46) and the large number of covariates (n=15). Therefore, it seems that RET-fusion status should at least have been considered for adjustment or patient selection. Most worryingly, an editorial in the Annals of Oncology concluded: *"After reviewing current data on selpercatinib* [LIBRETTO-001] *and comparing them with standard care in NSCLC, we have concluded that, while promising, the drug needs to be investigated in an RCT."*[40] This was partly on the basis of the findings of a retrospective analysis of 19 stage IIIB/IV lung adenocarcinoma patients with RET rearrangements treated with pemetrexed with or without combination therapy.[41] This study showed a PFS of 19 months (95% CI 12–not reached), very similar to that for selpercatinib in LIBRETTO-001 (21.95 months (95% CI: 13.8–NE) months). Of course, the EAG acknowledge that this is only one very small low-quality study not obtained by systematic review, but it does highlight the potential problem of lack of comparative evidence in the RET fusion-positive population.

In summary, the high risk of bias in a non-randomised between study comparison, the continued lack of balance of covariates and the possible omission of consideration of important prognostic covariates, including RET fusion status, constitutes a key issue.

3.4.2 Network meta-analysis (NMA)

3.4.2.1 NMA Methodology

For the NMA, both random effects and fixed effects models were assessed for all outcomes and the model which best fitted the data were used; in the base-case a random effects model was selected for all outcomes.

Only results from the NMA for the comparison with pembrolizumab with pemetrexed plus platinum chemotherapy and pemetrexed plus platinum chemotherapy were provided, although the NMA included more comparators, the reason provided by the company being that it was to support Health Technology Appraisal (HTA) processes in multiple countries.

Network diagrams were presented and are shown in Figures 3.14 to 3.16.

Figure 3.14: Network diagram for treatments included in the NMA for ORR

Based on Figure 13, CS[3]

ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; CS = company submission; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; ORR = overall response rate; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Figure 3.15: Network diagram for treatments included in the NMA for PFS

Based on Figure 15, CS[3]

ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PFS = progression-free survival; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Figure 3.16: Network diagram for treatments included in the NMA for OS

Based on Figure 17, CS[3]
ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; OS = overall survival; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Appendix D[8] described the methods of data imputation: for ORR, where n or N were missing, the other plus the proportion were used or the number randomised assumed for N. It was stated that if neither n or the proportion was reported then, if both complete response (CR) and partial response (PR) were reported, these were combined to attain the missing n. For survival, an HRs was required, which missing from only one study, RATIONALE 304, thus leading to the use of KM curves to reconstruct the IPD and thus estimate the HR.

3.4.2.2 NMA results

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

The results in each table below provide 1) the estimate for pemetrexed plus platinum chemotherapy versus selpercatinib derived from the propensity matching analysis, where the pemetrexed plus platinum chemotherapy arm data was derived from KEYNOTE-189 RCT, and 2) the estimate for pembrolizumab plus pemetrexed plus carboplatin/cisplatin versus selpercatinib, which was an indirect estimate based on a) the data for pembrolizumab plus pemetrexed plus carboplatin/cisplatin versus pemetrexed plus platinum chemotherapy, and b) the data for pemetrexed plus platinum chemotherapy versus selpercatinib derived from the propensity matching analysis. The effects for pembrolizumab plus

pemetrexed plus carboplatin/cisplatin versus pemetrexed plus platinum chemotherapy are not provided, as the intention is to provide only the results relating to selpercatinib. The results provided in the CS[3] are for the comparator versus selpercatinib. Therefore, the EAG has appended a column to provide the reciprocal result, which compares selpercatinib to the comparator (which would generally be regarded as the more standard approach for presentation of the results of a study drug relative to its comparators).

3.4.2.2.1 ORR

Both comparators had a significantly lower odds of an objective response than selpercatinib (Table 3.46).

Table 3.46: Relative treatment effect estimates expressed as pairwise ORs versus selpercatinib (with 95% CrI) for ORR, random effects model

Treatment	Pairwise OR (95% CrI) of comparators versus selpercatinib	Pairwise OR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 24, CS[3] CrI = credible interval; CS = company submission; OR = odds ratio; ORR = objective response rate		

3.4.2.2.2 PFS

Both comparators had a significantly higher hazard of disease progression than selpercatinib (Table 3.47).

Table 3.47: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for PFS, random effects model

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 26, CS[3] CrI = credible interval; CS = company submission; HR = hazard ratio; ORR = objective response rate		

3.4.2.2.3 OS

Both comparators had a significantly higher hazard of death than selpercatinib (Table 3.48).

Table 3.48: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for overall survival (OS), random effects model

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 28, CS[3] CrI = credible interval; CS = company submission; HR = hazard ratio; OS = overall survival		

3.4.2.3 Meta-regression

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

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

3.4.2.4 Assessment of inconsistency

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

The results of the inconsistency assessment are provided in Table 3.49 below. In all assessments the consistency of deviance information criterion (DIC) and residual deviance was similar (within the range of +/- 5 points) to the inconsistency of DIC and residual deviance. It is therefore concluded that no evidence of inconsistency was detected in the vast majority of analyses.

Table 3.49: Result of inconsistency assessment on the NMAs

Analysis	Consistency model		Inconsistency model		Number of data points
	Dbar	DIC	Dbar	DIC	
OS	26.58	48.22	27.90	51.57	31
PFS	26.38	48.16	26.97	50.81	28
ORR	45.69	86.76	43.28	85.76	51
Based on Table 29, CS[3] CS = company submission; Dbar = mean sum of residual deviances; DIC = deviance information criterion; NMA = network meta-analysis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival					

EAG comment:

- The EAG considers that the NMA was conducted generally adequately. However, given the lack of justification for the choice of pemetrexed plus platinum chemotherapy and the KEYNOTE-189 trial, in the clarification letter, the EAG requested that NMA sensitivity analyses be conducted with different "pseudo-comparators" i.e., ITCs with different comparators in order to connect with the network, to which the company responded, "*As outlined in response to A21 above, and as mentioned in Section B.2.8.1 of the Company Submission, KEYNOTE-189 was the only trial to provide IPD and the pemetrexed plus platinum chemotherapy was used as a pseudo-comparison because Lilly only had permission to use IPD from this arm of the KEYNOTE-189 trial. As discussed in response to Question A23, imbalances in baseline characteristics caused by RET-fusion positive patients typically being younger and healthier than NSCLC patients as a whole means that population-adjusted methods such as a MAIC would reduce the available sample size and introduce uncertainty and potentially bias to the analyses. As such, an IPD method has been selected and the use of a population adjusted approach is not presented. As noted above, the lack of available IPD mean it is not possible to conduct an ITC with comparators other than pemetrexed plus platinum chemotherapy*." A detailed critique of the ITC and the use of KEYNOTE-189 can be found in Section 3.4.5.1.
- As mentioned in Section 2.3, the EAG does not accept that all comparators in the scope were included for the non-squamous population. Given the lack of reporting of results, in the clarification letter the EAG requested that for all outcomes for which a NMA was conducted (and for any further NMAs requested in A19), there should be a grid detailing the NMA treatment effect estimates (HRs and ORs) for all permutations of treatment comparisons involved in the network, as well as a ranking of all treatments involved in the network. The company responded by stating that, "*The NMA which analysed OS, PFS and ORR to provide relative treatment effect estimates of comparative efficacy between selpercatinib and comparators was conducted from a Global perspective to inform reimbursement activities across various geographies. As such, additional comparators that are not relevant to the UK setting were included. Given their lack of relevance to the current submission (see response to Question A9 for further detail), an updated network diagram for each outcome that includes these other treatment options has not been provided…. As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal….. As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal*." The EAG considers that the company's rationale for excluding other comparators is weak, based as it is upon clinical opinion. A better approach would have involved the inclusion of all feasible comparators in the NMA. This would have led to the same conclusion that selpercatinib is the best treatment, if the expert opinion that these comparators are inferior is true. However, NMAs and other rigorous methods of comparison exist for the very reason that expert opinion is often inaccurate. Therefore, if the clinical opinion that the comparators are inferior is false, then it is possible that a more inclusive NMA may have produced a result that contradicts the NMA result presented in the CS. Therefore, this is a key issue (see Section 2.3).
- As already stated in Section 3.3, all three studies, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan, that compared pembrolizumab plus pemetrexed plus platinum chemotherapy to pemetrexed plus platinum chemotherapy were included in the NMA to indirectly estimate the treatment effect of the former versus selpercatinib given that an ITC was used to estimate the treatment effect of the latter versus selpercatinib.[17, 18, 20] This means that any heterogeneity and trial selection for pooling will have implications for the comparison between

selpercatinib and the pembrolizumab combination. One source of heterogeneity that may exist between comparisons in the network is RET fusion-positive status. Information on RET fusion-positive status was not provided for those three trials. Since the vast majority (98%) of people with NSCLC are RET-fusion negative, a sample where RET-fusion status is not defined is highly likely to have a preponderance of RET fusion-negative participants. Therefore, it is probably that the three trials would possess mostly RET fusion-negative status. They would therefore be very different to LIBRETTO-001 SAS1, where all patients are RET fusion-positive. Such a difference in RET fusion status between comparisons will be a problem if RET fusion status has the capacity to affect outcome. As explained in Section 3.4.1.5, the company does not think that RET-fusion status is independently prognostic, because the effect of this variable on outcome became non-significant after adjustment for factors with which it was believed to correlate. However, although a lack of a true effect is one conclusion that can be drawn to explain the null effect, another possible cause is a lack of statistical power in the analysis. This is highly likely given the large ratio of covariates to sample size in the regression, in conjunction with the persistence of a point-estimate of clinically important magnitude. Given the possibility, therefore, that RET fusion-positive status is indeed a treatment effect modifier, the high likelihood that RET-positive status is different between these trials creates a concern about the validity of the NMA, a solution for which would be and RCT in the RET fusion-positive population (see Section 3.2.8).

- In Section 3.3, Tables 3.35 and 3.36 summarise the baseline characteristics of the LIBRETTO-001 study and the three studies used for comparison B. These tables do not demonstrate any clear clinical heterogeneity between the four studies (and thus comparisons A and B) for most variables, but there appear to be differences in the source of patients. The KEYNOTE-189 Japan study comprised participants who were all from Japan, whereas the other studies did not. Therefore, clinical heterogeneity may also have arisen from differing ethnicity/clinical practice, as well as differing RET fusion-status, which raises further concern regarding heterogeneity in the NMA.
- The company also did not present the outcomes separately for each of the three trials for the comparison of pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy. The EAG have therefore compiled these for OS and PFS in Table 3.50.
- The point estimates in Table 3.50 seem to indicate some heterogeneity of outcomes, the implications of which have not been explored directly in the CS i.e., by testing the effect of excluding any of the studies from pooling. This is therefore explored in Section 3.5.
- There is no evidence that an NMA or any kind of comparative analysis was performed for the outcome of AEs. This is a key issue as it prevents the Committee being able to properly weigh up the benefits against the potential harms of pembrolizumab.

Table 3.50: Relative treatment effect estimates expressed as HRs of pembrolizumab plus pemetrexed plus platinum chemotherapy versus. pemetrexed plus platinum chemotherapy

Trial	OS HR (95% CrI)	PFS HR (95% CrI)
KEYNOTE-189 (N=616)	0.49 (0.38,0.64)	0.52 (0.43,0.64)
KEYNOTE-189 Japan (N=40)	0.29 (0.07,1.15)	0.62 (0.27,1.42)
KEYNOTE-021 (N=123)	0.90 (0.42,1.91)	0.53 (0.31,0.91)

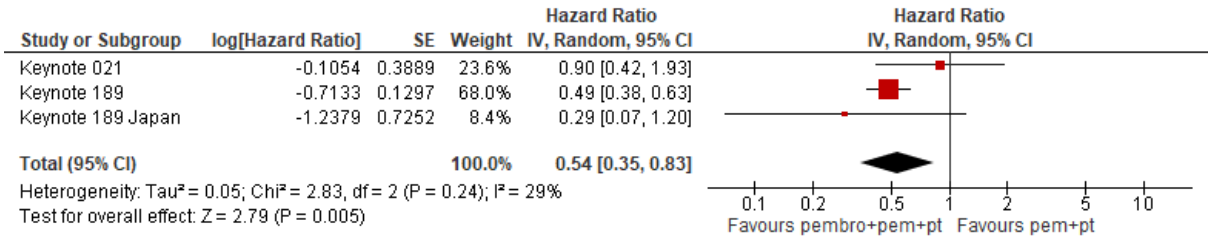
Based on Gandhi et al 2018, Langer et al 2016, Horinouchi et al 2021[17, 18, 20]
CrI = credible interval; HR = hazard ratios; OS = overall survival; PFS = progression-free survival

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG performed a meta-analysis of the trials of pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy for the outcomes of OS and PFS.

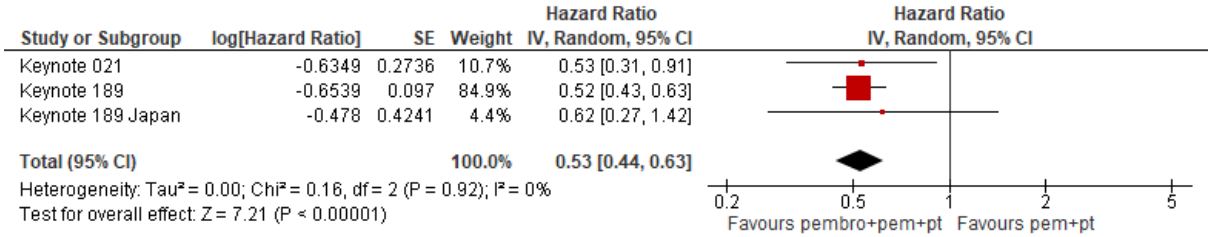
Statistical testing for heterogeneity yielded an I^2 of 29% for OS (Figure 3.17) and 0% for PFS (Figure 3.18). Therefore, most of the point estimate differences within each outcome could be argued to be explained by sampling error rather than the effects of any outcome modifiers. Nevertheless, given the likely differences in RET fusion status between studies, and the definite differences between studies in ethnicity, the possibility remains that the clear point estimate differences are at least partially driven by these covariates and that it is a lack of statistical power that prevents more significant I^2 values. Therefore, heterogeneity of trials in the NMA has been identified as a key issue.

Figure 3.17: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS



CI = confidence interval; OS = overall survival; PEM = pemetrexed; PEMBRO = pembrolizumab; PT = platinum

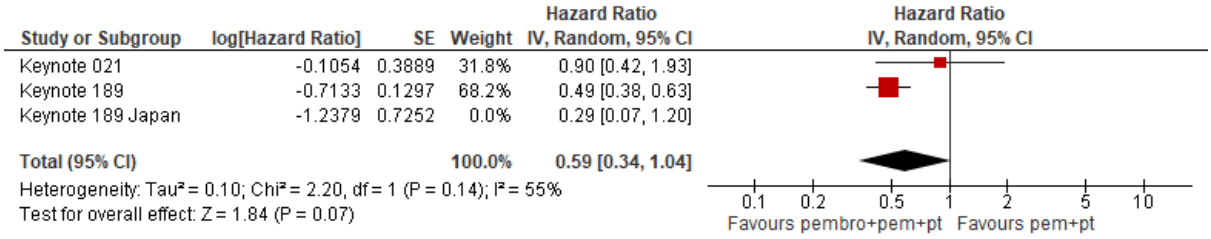
Figure 3.18: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS



CI = confidence interval; PEM = pemetrexed; PFS = progression-free survival; PEMBRO = pembrolizumab; PT = platinum

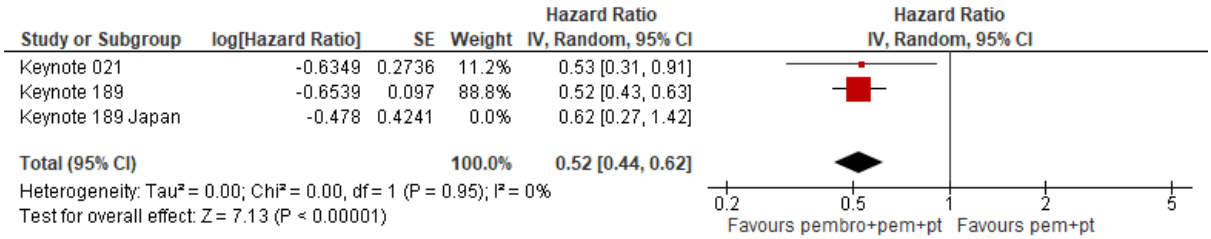
As a sensitivity analysis, the EAG removed the KEYNOTE-189 Japan study from the meta-analyses for both outcomes. The decision to remove this study was made for two reasons. Firstly, KEYNOTE-189 Japan was the greatest outlier for the main outcome of OS. Secondly, the EAG agreed that the most likely source of clinical heterogeneity within these three studies was ethnicity, because it was known that the KEYNOTE-189 Japan population were exclusively Japanese nationals, whereas the other two studies comprised <10% Asian participants. Therefore, given that clinical heterogeneity was most likely to result from different ethnicity in KEYNOTE-189 Japan, removing the KEYNOTE-189 Japan study was deemed the most likely way to reduce such heterogeneity. As Figure 3.19 shows, the removal of KEYNOTE-189 Japan reduced the magnitude of the OS effect from 0.54 to 0.59. Although this difference may not appear large, the EAG would prefer to see this revised estimate used in the NMA, as it may have an important knock-on effect on cost-effectiveness. Therefore, possible NMA heterogeneity is a key issue.

Figure 3.19: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS, with the effects from KEYNOTE-189 Japan not included in the pooled result



CI = confidence interval; OS = overall survival; PEM = pemetrexed; PEMBRO = pembrolizumab; PT = platinum

Figure 3.20 Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS, with the effects from KEYNOTE-189 Japan not included in the pooled result



CI = confidence interval; PEM = pemetrexed; PEMBRO = pembrolizumab; PFS = progression-free survival; PT = platinum

3.6 Conclusions of the clinical effectiveness section

The CrIs yielded by the ITC and the NMA suggested that selpercatinib was significantly more effective in terms of ORR, PFS and OS than pemetrexed plus platinum chemotherapy and pembrolizumab plus pemetrexed plus carboplatin/cisplatin respectively. In all cases the point estimates could be regarded as being of a clinically significant magnitude. However, the validity of these results is in question for several reasons.

Firstly, the methodology used for adjusting of the pseudo-comparator arm to resemble the selpercatinib trial more closely may not have been optimal. Of the adjustment methods explored, it appears that the default PSM method led to the most conservative results, which supports the use of this method. However, because the array of methods explored by the company were limited, it is possible that unexplored methods (such as addition of multivariate regression on the matched sample) may have yielded results that were less favourable to selpercatinib than those observed by the default PSM approach. Most crucially, important prognostic factors might have been omitted, including RET fusion status, which some observational data in the RET fusion-positive population shows might seriously underestimate the effectiveness of the pemetrexed containing comparators. Secondly, the validity of the NMA results partly depend upon the validity of the choice of data for the pseudo-comparator arm. The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm is stated as being due to relevant IPD not being available from any other sources, which the EAG consider to be not a convincing rationale. It is likely that had other sources of pemetrexed plus platinum chemotherapy data been used then very different overall NMA results might

have been yielded. Both of these problems are a direct result of using one-arm trial data for selpercatinib. Had the company waited until the results of the randomised LIBRETTO-431 trial are complete, then these two issues would have been avoided, and there would have been far less risk of selection bias.

Applicability of the results is also under question. The lack of data on the characteristics of the UK target population means that it cannot be assumed that the trial participants were comparable to the target population. Given the array of potential effect modifiers shown by the sub-group analyses, it is possible that effects observed in the trial would not be the same as those that would be observed in the target population. In addition, there are suggestions that the subsequent therapies used in the trial would differ from those use in UK clinical practice. Again, this could lead to trial results that are not applicable to the target population, as well as producing a bias in the treatment effect.

The limited array of comparators in the decision problem (two) may also have influenced interpretations. Had other comparators been present, as requested by the NICE scope, selpercatinib may not have emerged as the most effective treatment. In this context, the important question for consideration is whether the limited array of comparators makes clinical sense, given the population of the decision problem, which is RET fusion-positive non-squamous NSCLC in the context of NG122. Even if the two comparators are agreed to be the only options that fit with this population, a further question is whether the evidence can be applicable to the broader population that includes squamous histology.

Finally, the quality of AE data was seriously compromised by there being no specific AE data for the participants fitting the decision problem definition. It is possible that the pattern AEs in this smaller group would be different to those in the wider group that were analysed. It is also the case that no NMA or any form of comparative analysis was carried out for AEs, preventing a rigorous assessment of benefits and harms.

4. COST-EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

A systematic literature search was performed to identify cost-effectiveness studies (CS, Appendix G).[8] No searches were conducted to identify health-state utility values (HSUV), and cost and healthcare resource use studies.

4.1.1 Searches performed for cost-effectiveness section

The following paragraphs contain summaries and critiques of searches related to cost-effectiveness presented in the CS.[3, 8] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[10, 11] The CS was checked against the STA specification for company/sponsor submission of evidence.[12]

Appendix G of the CS reported the literature searches used to identify cost-effectiveness studies.[8] Searches were conducted in March 2019. The searches were not updated.

A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for the cost-effectiveness literature review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE and MEDLINE in-Process & E-pubs ahead of print	Ovid	Not reported	04/03/2019
Embase	Ovid	1974-1 March 2019	04/03/2019
EconLit	Ovid	1886-21 February 2019	04/03/2019
Health Technology Assessment (HTA) Database	Centre for Reviews and Dissemination (CRD) interface	2016-2019	04/03/2019
National Health Service Economic Evaluation Database (NHS EED)	Centre for Reviews and Dissemination (CRD) interface		04/03/2019

EAG comment:

- The CS provided details of the literature searches for the EAG to appraise.[3, 8]
- Searches were conducted to identify cost-effectiveness analyses.
- The cost-effectiveness searches were conducted in March 2019. Update searches were not conducted, so the searches were more than 3 years out of date. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since March 2019. In response to clarification, the company explained that *'Due to time and resource constraints, an update to this SLR could not be completed in time for submission. Lilly do not anticipate that an updated will significantly impact the current decision problem or cost-effectiveness assessment. In addition, the publication of recent NICE appraisals for selpercatinib in the second line (TA760) and pralsetinib (TA812) in a similar*

indication provides confidence that the most relevant information for economic modelling is already available.'[13]

- No searches were conducted to identify HSUVs, and cost and healthcare resource use studies.
- The CS explained that utility values were obtained from the LIBRETTO-001 trial, so '*it was not deemed necessary to extract quality of life data from the economic SLR*' (Appendix H.1).[8]
- The CS reported in Appendix I.1 that cost and healthcare resource use searches were not conducted because the values used in their model were *'based on previously accepted values from prior NICE appraisals in NSCLC and validated by UK clinical experts'*.[8]
- A good range of databases were searched. Full details of the database searches, including the database name, host platform, and date searched, were provided.
- Conference proceedings and HTA organisation websites were searched, but full details of these searches were not reported. Full details of the HTA organisation website searches and a list of conferences of interest were provided in the response to clarification.[13]
- The database search strategies were well structured. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE).
- The search strategies were not well reported, and so were not reproducible. The main issue with the database search strategy reporting related to the Boolean operator AND being replaced by an ampersand. The EAG assumes that the searches were conducted correctly as the results of each search line, and the final total of records retrieved, were provided.
- There were no language or date limits for all but one of the database searches. The MEDLINE search strategy was limited by date to '2000-current'. The CS did not report why this date limit was included in the MEDLINE search.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as Item 8 of the PRISMA-S reporting checklist recommends.[14] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[15]
- Study design search filters for cost-effectiveness were included. The search filters were not cited, as current practice recommends.[14]
- MeSH terms rather than EMTREE terms were incorrectly included in the Embase search strategy (Table 42).

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost-effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (≥18 years) with advanced/metastatic EGFR mutation positive NSCLC	Patients with intermediate-stage NSCLC
Intervention	Approved or investigational novel pharmacological interventions evaluated as first-line therapy (monotherapy or	Surgery or radiotherapy only

	Inclusion criteria	Exclusion criteria
	combinations with any other treatments will be included)	
Comparator	Any intervention or BSC	No exclusions
Outcomes(s) 1 (Published economic evaluations)	No limit	No exclusions
Outcomes(s) 2 (HRQoL studies)	No SLR conducted for HRQoL	No SLR conducted for HRQoL
Outcomes(s) 3 (Cost/resource use studies)	No SLR conducted for cost/resource use	No SLR conducted for cost/resource use
Study design 1 (Cost-effectiveness analysis studies)	Cost-effectiveness analyses Cost-utility analyses Cost-consequence analyses Cost-benefit analyses Cost-minimisation analyses Budget impact models	Studies only reporting costs will be excluded
Study design 2 (HRQoL studies)	No SLR conducted for HRQoL	No SLR conducted for HRQoL
Study design 3 (Cost/resource use studies)	No SLR conducted for cost/resource use	No SLR conducted for cost/resource use

Source: Table 46, Appendices.[8]
BSC = best supportive care; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; NSCLC = non-small-cell lung cancer; SLR =systematic literature review

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost-effectiveness studies.

4.1.3 Conclusions of the cost-effectiveness review

The CS provides an overview of the included cost-effectiveness studies, but no specific conclusion was formulated. No searches were conducted to identify utility and resource use and costs studies.

EAG comment: Eligibility criteria were suitable for the SLR performed and the review for cost-effectiveness studies was performed adequately. However, searches to identify utility and resource use and costs studies were not conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Not consistent with reference case (no review used to identify HRQoL studies)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Consistent with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear whether the UK tariff was used
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

EAG = Evidence Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; NHS = National Health Service; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALYs = quality-adjusted life years; UK = United Kingdom

4.2.2 Model structure

In line with a number of prior NICE appraisals in NSCLC (TA760, TA705 and TA683)[7, 21, 42], a cohort partitioned survival model (PSM) was developed including three mutually exclusive health states: a progression-free state, a progressed disease state, and death:

- Progression-free: Patients' disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment acquisition, administration, treatment monitoring, medical management of the condition and the management of Grade 3/4 AEs. Patients also experience a higher utility compared with progressed disease.
- Progressed: Patients have met the RECIST v1.1 criteria for disease progression. Patients in this state may continue their allocated therapy for a time and/or have subsequent anti-cancer therapy

and incur costs associated with treatment acquisition, administration, medical management of the condition and terminal care. Patients experience a lower utility compared with progression-free disease

- Dead: Patients no longer incur costs, life years or utilities.

Patients were modelled to enter the model in the progression-free health state. Cumulative survival probabilities from PFS and OS parametric survival functions were then used to determine the proportion of patients in each heath state at each model cycle. The model was developed in Microsoft Excel.

A lifetime horizon (i.e., 25 years) with a cycle length of 1 week was applied to ensure all costs and QALYs were captured.

EAG comment: The main concern of the EAG relates to the use of a partitioned survival model without exploring a state transition model (STM) approach alongside it. The NICE DSU TSD19 recommended the use of STMs alongside PSMs to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period. This was not done by the company, and the EAG was concerned that the chosen PSM may not be fully validated. In response to clarification question B1, the company acknowledged that a PSM approach assumes that the modelled survival endpoints are structurally independent and that this may represent a limitation of the selected approach. The company further acknowledged that the PSM approach may over- or under-estimate long-term outcomes if the HR calculated from the observed period does not accurately reflect the expected HR in the extrapolated period. Nevertheless, the company argued that PSM and STM estimates typically converge as the data mature and prior NICE appraisals of oncology treatments indicated that the choice of a PSM or STM approach typically has a limited impact. However, PFS and OS data for selpercatinib from LIBRETTO-001 were relatively immature at the June 2021 data cut-off (42% had progressed and [redacted] had died), and the large majority of (PF)LY gains were accumulated beyond the observed data period. Hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B23). To assist in verifying the plausibility of the PSM extrapolations, the EAG would like to see the outcomes of a STM.

4.2.3 Population

The population considered in the CS was treatment-naïve patients with advanced non-squamous RET fusion-positive NSCLC who require systemic therapy, which is narrower than the population defined in the final NICE scope.

The modelled baseline patient characteristics were presented in Table 38 of the CS. These were based on the baseline characteristics of patients who received selpercatinib in the LIBRETTO-001 trial and were considered representative of patients in UK clinical practice.

The key baseline patient characteristics in the economic model are listed in Table 4.4 below.

Table 4.4: Key baseline patient characteristics used in the economic model

Model parameter	Value	Source
Mean age (years)	[redacted]	LIBRETTO-001 (SAS1)
Female (%)	62.3	LIBRETTO-001 (SAS1)
Mean weight (kg)	[redacted]	LIBRETTO-001 (SAS1)
Based on CS Table 38 CS = company submission		

EAG comment: The main concern of the EAG relates to the modelled population being narrower than the population defined in the NICE scope. Although the population defined in the NICE scope is *adults with untreated advanced RET fusion-positive non-small cell lung cancer (NSCLC)*, the company stated in Table 1 of the CS that the evidence presented in the submission is for patients with non-squamous histology. In response to the clarification letter, the company stated that, whilst squamous histology was not an exclusion criterion for enrolment in the LIBRETTO-001 trial, owing to the rarity of RET fusion-positive squamous histology, no squamous patients were enrolled into the SAS1 population. In addition, the company argued that clinical experts were expected to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. Notwithstanding the advice from clinical experts, the EAG does not think it is ideal that recommendations are applied to populations other than those on whom selpercatinib has been trialled. More details regarding this issue are provided in Section 2.1

4.2.4 Interventions and comparators

The intervention considered in the CS was selpercatinib. In line with the existing licensed dose in advanced pre-treated RET fusion-positive NSCLC, selpercatinib (160 mg) was administered orally twice daily in 28-day cycles until PD or unacceptable toxicity, or any other reasons for treatment discontinuation.

The comparators considered were pembrolizumab combination therapy (pembrolizumab [200 mg] plus pemetrexed [500 mg/m^2] plus platinum chemotherapy [carboplatin AUC 5 mg/ml x min]) and pemetrexed (500 mg/m^2) plus platinum chemotherapy (carboplatin AUC 5 mg/mL x min). Pembrolizumab was given in 21-day cycles up to 2 years or until disease progression, carboplatin was given up to 4 x 21-day cycles (6 x 21-day cycles in the pemetrexed plus platinum chemotherapy arm) or until disease progression, and pemetrexed was given up to disease progression.

Several comparators listed in the NICE scope (described in Table 1 of the CS) were not considered in the current submission. The company stated that, as the target population has been restricted to patients with non-squamous histology, comparators relevant to the squamous population were not included in the submission. Pralsetinib was not considered a relevant comparator in this population as it has not received a positive recommendation from NICE, and therefore was not considered part of routine practice. In addition, the company argued that patients with a positive RET status are most commonly treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab plus pemetrexed with platinum-based chemotherapy, and as such, these were the only comparators considered relevant to this submission.

EAG comment: The main concern of the EAG relates to comparators listed in the NICE scope that were not considered in the current submission. Pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment were not included as comparators, although they were all included in the scope, as well as the NG122 care pathway. In response to the clarification letter, the company stated that comparator choice was informed by feedback received from expert oncologists practicing in the NHS and supported by an RWE study to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected. The EAG also asked the company to conduct all effectiveness analyses, whether by ITC or NMA or combination (as in the CS), and cost-effectiveness analyses including all comparators in the scope and the NG122 care pathway. The company did not provide any of these. The EAG was not satisfied with the company's response

and concluded that the company rejected NICE-recommended comparators based on clinical opinion and an arbitrary selection of evidence. More details regarding this issue are provided in Section 2.3.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 1 week with a lifetime time horizon (25 years).

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for selpercatinib is the single-arm LIBRETTO-001 study. The SAS1 analysis set of this study was used to populate the model. The company considered this to be representative of patients in UK clinical practice.

A propensity score matching approach based on the KEYNOTE-189 study was used to compare selpercatinib with a matched reference arm for pemetrexed plus platinum chemotherapy. The pembrolizumab combination therapy was modelled through the application of a HR to the pemetrexed plus platinum chemotherapy reference arm extrapolation that was generated through an NMA.

The main outcomes for treatment effectiveness were PFS and OS. The company stated that the criteria considered for determining the best parametric fit were: 1) goodness-of-fit statistics (AIC and BIC); 2) assessment of visual fit to the observed KM curve; and 3) clinical expert opinion regarding the plausibility of the long-term extrapolations of each function.

4.2.6.1 Company's base-case parametric curves for PFS, OS and TTD

4.2.6.1.1 PFS

To estimate long-term PFS for selpercatinib and comparators, PFS data generated for selpercatinib, and the matched reference arm (pemetrexed plus platinum chemotherapy) were extrapolated through applying parametric survival functions. Progression-free survival for pembrolizumab combination therapy was then constructed through applying a HR as generated through the NMA.

As part of the survival analyses for PFS, the following parametric functions were explored:

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

The company argued that because of the short duration of follow-up all curves had a similar visual and statistical fit (as measured by Akaike information criterion (AIC) and Bayesian information criterion (BIC)), and hence argued that it was not possible to specify an optimal curve choice based on visual and statistical fit. Therefore, clinical feedback from UK-based expert oncologists on the long-term validity of the survival curves was sought. In addition, the company cited a physician stating that the effectiveness of selpercatinib in RET fusion-positive patients was comparable to those of ALK-positive patients treated with targeted therapies. Based on feedback from UK-based expert oncologists and the comparison with ALK-positive patients treated with targeted therapies, the Gompertz curve was selected to model PFS for selpercatinib and pemetrexed plus platinum-based chemotherapy. Progression-free survival for the pembrolizumab combination therapy arm was modelled by applying

the HR (0.517 [0.401, 0.681]) from the NMA to the pemetrexed plus platinum-based chemotherapy arm.

4.2.6.1.2 OS

To estimate long-term OS for selpercatinib and comparators, OS data generated for selpercatinib, and the matched reference arm (pemetrexed plus platinum chemotherapy) were extrapolated through applying parametric survival functions. The OS for pembrolizumab combination therapy was then constructed through applying a HR as generated through the NMA.

As part of the survival analyses for PFS and OS, the following parametric functions were explored:

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

In line with PFS, the company argued that it was not possible to select the optimal curve based on visual or the statistical fit and clinical feedback was sought. Based on clinical expert opinion, the company selected the spline knot 1 model for the modelling of OS in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms. The HR from the NMA (0.610 [0.489, 0.761]) was then applied to the pemetrexed plus platinum-based chemotherapy arm to model OS for the pembrolizumab combination arm.

4.2.6.1.3 TTD

To estimate the duration of treatment for selpercatinib, TTD was modelled in line with the approach taken for PFS and OS. Time to treatment discontinuation for the comparators was modelled using the selpercatinib PFS curve for the intervention, capped at a maximum number of cycles (where specified in the SmPC). The company considered this to be a conservative approach.

For the modelling of selpercatinib TTD, an exponential curve was selected in the company's base-case. The company argued that the exponential curve was the best fitting curve (based on AIC and BIC) and was deemed clinically plausible due to it lying above the PFS landmark estimates, in line with feedback from clinical expert oncologists which suggested treatment would continue for a short period post-progression. Table 4.5 reports further detail regarding the criteria for the choice of survival curves for PFS, OS and TTD.

Table 4.5: Criteria for the choice of survival curves

	PFS	OS	TTD
General considerations	**Pemetrexed plus platinum chemotherapy** Modelled by applying the same parametric curve as for selpercatinib. **Pembrolizumab combination therapy** Modelled by applying the HR resulting from the NMA.	**Pemetrexed plus platinum chemotherapy** Modelled by applying the same parametric curve as for selpercatinib. **Pembrolizumab combination therapy** Modelled by applying the HR resulting from the NMA.	**Pemetrexed plus platinum chemotherapy** TTD was modelled using PFS. **Pembrolizumab combination therapy** TTD was modelled using PFS.
Statistical fit to the observed data (based on AIC and BIC)	**Selpercatinib** The AIC indicates that the split knot 3 curve has the best statistical fit. The BIC indicates that the log-logistic curve has the best statistical fit.	**Selpercatinib** AIC and BIC indicate that the log-normal curve has the best statistical fit.	**Selpercatinib** AIC and BIC indicate that the exponential curve has the best statistical fit.
Visual fit to the observed data	The company considered all curves to have a similar visual fit in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms.	The company considered all curves to have a similar visual fit in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms.	The company considered all curves to have a similar visual fit in the selpercatinib arm.
Fit to observed data (from the LIBRETTO-001 trial)	The loglogistic and lognormal curve was excluded as selpercatinib PFS remained unrealistically high ([redacted] and [redacted] after 20 years). The spline knot 3 curve was excluded as PFS started to increase again.	Not discussed by the company	**Selpercatinib** The mean TTD after PFS was [redacted].
Clinical plausibility of the extrapolation (based on comparison with historical data)	One clinical expert stated that selpercatinib estimates in *RET* fusion-positive patients could be deemed comparable to those of *ALK*-positive patients treated with targeted therapies. Median PFS for two such therapies were found to be 24.02 months (brigatinib) and 34.8 months.[43, 44] All parametric curves resulted in a median survival between 23 and 27 months.	Tan *et al.* reports a median OS (49.3 months) for *RET* fusion-positive NSCLC patients treat with selective *RET* tyrosine kinase inhibitor.[45] The stratified lognormal curve (median survival 49.94 months) results in the lowest difference to results of this study Another study reported a median OS for the *ALK-1* inhibitor alectinib (48.2 months). The lognormal curve and the spline knot 1 curve (median survival 48.33 months) result in the lowest difference to the results of this study.	Not discussed by the company.
Clinical plausibility of the extrapolation (based on clinical expert opinion)	**Selpercatinib** The median PFS of the log-normal curve was closest to that produced by expert opinion (21 months).	**Selpercatinib** The median OS of the exponential curve [redacted] was closest to the mean (61 months) based on expert opinion.	**Selpercatinib** Experts stated that patients who progress often remain on treatment until they have

	PFS	OS	TTD
	Pemetrexed plus platinum chemotherapy The median PFS of the spline knot 3 curve [redacted] was closest to the mean based on expert opinion (6–11 months). None of the curves resulted in PFS values that were in the range specified by experts. **Pembrolizumab combination therapy** The median PFS of the exponential and the Gompertz curves [redacted] was closest to the mean (10.5 months) based on expert opinion (10-11 months). None of the curves resulted in PFS values that were in the range specified by experts.	**Pemetrexed plus platinum chemotherapy** The median OS of the spline knot 2 and stratified Gompertz curves was 12.2 months while the mean of the exponential and unstratified Gompertz curves was 12.43 months. The OS of these four curves fall into the range of expected OS based on expert opinion (12-24 months). **Pembrolizumab combination therapy** All curves resulted in OS values that were in the range specified by experts (12-24 months).	received a further two scans, with approximately 3 months between each scan.
Base-case approach	Unstratified Gompertz	(Unstratified) spline knot 1	Unstratified Exponential

AIC = Akaike information criterion; ALK = anaplastic lymphoma kinase; BIC = Bayesian information criterion; HR = hazard ratio; NMA = network meta-analysis; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection; TTD = time to treatment discontinuation

EAG comment: The main concerns of the EAG relate to: a) immaturity of the LIBRETTO-001 survival data; b) survival curve choice transparency; c) no treatment waning; d) underestimation of the comparator PFS compared to the LIBRETTO-001 trial; e) substantial differences between modelled TTD and observed median TTD after progression and f) substantial differences of comparator PFS compared to alternative sources.

a) Data from the LIBRETTO-001 trial for the modelling of PFS and OS for selpercatinib were relatively immature (42% had progressed and [redacted] had died), adding substantial uncertainty to the extrapolated survival data in the economic model. In addition to the company's scenario analyses in the CS, the EAG conducted scenario analyses to explore a range of plausible PFS and OS curves. Plausibility was based on 1) the curve being closer to an expert estimate or external data than the curve chosen by the company, and 2) the curve having a plausible shape. Scenario analyses for the comparison with pembrolizumab combination therapy resulted in the net monetary benefit (NMB) ranging between £39,808 (Gompertz for PFS and stratified Gompertz for OS) and £67.101 (exponential curves for PFS and OS). Scenario analyses (conditional on the EAG base-case) for the comparison with pembrolizumab combination therapy resulted in the NMB ranging between £39,808 (Gompertz for PFS and stratified Gompertz for OS) and £67,101 (exponential curves for PFS and OS). Scenario analyses for the comparison with pemetrexed plus platinum chemotherapy resulted in the NMBs ranging between -£36,197 (Gompertz for PFS and stratified Gompertz for OS) and -£8,192 (exponential for PFS and OS). The EAG's scenario analyses resulted in a wide range of NMBs, which confirms the substantial uncertainty surrounding the extrapolated survival data.
b) The EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent: The EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent:
    a. Next to the standard parametric models, the company also considered complex parametric survival curves (i.e., spline models) for the modelling of PFS and OS and implemented the spline knot 1 model for the modelling of OS in its base-case. The NICE DSU TSD 21 guidance states that more complex survival curves should be considered when hazard functions are observed, or expected in the longer-term, to have complex shapes (i.e., where there are two or more turning points, or where there are two or more important changes in the hazard function slope). However, based on the presented evidence, it was unclear to the EAG why the company selected a spline model for the modelling of OS rather than a standard parametric model. Upon request for clarification, the company argued that complex curves were added 'in the interest of maximising clinical plausibility', which, according to the EAG, does not justify why standard parametric curves were insufficient for the modelling of OS.
    b. To examine the diagnostics of the parametric survival models based on the observed data, the EAG requested plots for standard normal quartiles versus log time and log survival odds versus log time. The company did not provide these plots, stating that they were not available.
    c. Due to the immaturity of data, the company considered the visual and statistical fit of parametric survival curves to the KM data an insufficient basis for the selection of the most appropriate survival curves. Expert opinion was therefore sought to inform the choice of survival curves. However, Table 4.5 highlights that the company's selected survival curves were not always those closest to the expert inputs. For example, the company modelled PFS using an unstratified Gompertz curve, but the median survival

resulting from this curve was not closest to the expert inputs for selpercatinib or pemetrexed plus platinum chemotherapy. It was not clear to the EAG why the company did not select the curves that were closest to the expert inputs.

d. The modelled PFS and OS values as reported in CS, Tables 41 and 44 do not match with the values informing PFS and OS in the economic model for several survival curves, including the company's base-case. The EAG was unable to identify the source of this mismatch and the potential impact on the cost-effectiveness results is unclear. This mismatch and the opacity relating to its source add to the lack of transparency in the choice of survival curves.

The non-transparent survival model selection, in addition to the immaturity of the LIBRETTO-001 trial data, adds substantial uncertainty to the extrapolated PFS, OS, and TTD data. As highlighted in the scenario analyses described in EAG comment a) and Section 6.1.2, the range of NMBs varies by up to £28.000.

c) The company assumed that there was no waning of the selpercatinib treatment effect in its base-case. Rationale was provided in CS, Table 36, suggesting that the selected OS and PFS parametric survival curves were validated by UK clinical experts on the most clinically plausible long-term efficacy estimates. In clarification question B10a the EAG requested further justification as to why no treatment waning was considered. The EAG also requested HR plots for PFS and OS versus time for both comparisons, as well as an updated economic model and scenario analyses exploring treatment waning kicking in at different time points. The company highlighted that there was no evidence of relative treatment waning in the single-arm LIBRETTO-001 trial for selpercatinib. In addition, the company argued that different assumptions on the long-term treatment effect would have been implicitly captured in the selected survival curves, that patients with RET fusion-positive advanced NSCLC have a poor prognosis, and that selpercatinib is a continuous, treat to progression treatment. Although plots of the smoothed hazard rates per arm were provided in response to the clarification letter, the company did not provide HR plots and did not provide scenario analyses exploring treatment waning in an updated economic model. The EAG would like to stress that these analyses are important for the assessment of the potential impact of treatment waning on the cost-effectiveness results, especially given that the current PFS and OS data are immature.

d) Based on the company's response to clarification question B23, the EAG noticed that the observed PFS for pemetrexed plus platinum chemotherapy (based on the 1.0 year or 1.5 years truncation points) is larger than the modelled PFS based on a lifetime time horizon. This suggests that the modelled PFS for pemetrexed plus platinum chemotherapy is underestimated and hence, the PFS increments for selpercatinib versus pemetrexed plus platinum chemotherapy are potentially overestimated in favour of the intervention.

e) In its base-case the company selected their optimal curve for the modelling of TTD based on its statistical and visual fit to the KM data, arguing that this was appropriate given the maturity of TTD data. The company selected the exponential curve, which resulted in a median TTD of [redacted] compared to a median modelled PFS of [redacted] months. This is not in line with clinical experts' inputs, which stated that patients are usually treated until approximately 3 months after progression. This was confirmed by the mean post progression TTD in the LIBRETTO-001 trial, which was [redacted]. The EAG therefore requested a scenario analysis in which TTD would be more in line with clinical experts' expert inputs and the post progression TTD in the LIBRETTO-001 trial. The company provided this analysis which decreased, the NMB by approximately £2,000, in each comparison.

f) Based on the company's PSM approach, median PFS for patients treated with pemetrexed plus platinum chemotherapy was approximately [redacted] months. The EAG, however, identified a

retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (like both comparators)[41]. The EAG, however, identified a retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (as with both comparators). Based on this evidence, the EAG considers the modelled effectiveness of pemetrexed plus platinum chemotherapy to be potentially underestimated, and hence the treatment effect of selpercatinib versus pemetrexed plus platinum chemotherapy overestimated.

4.2.7 Adverse events

The main sources of evidence used to inform AEs incidence rates were the LIBRETTO-001 trial for selpercatinib and the KEYNOTE-189 trial for the comparators.[3] The economic model included all Grade 3-4 AEs with at least 2% difference in reported frequency in the source trials between interventions (CS, Table 49). The consequences of AEs were modelled in terms of costs and utility decrements.

EAG comment: The main concerns of the EAG relate to: a) the approach of including AEs with at least a 2% difference in frequency between interventions in the included trials, b) mismatches between values related to AEs in the CS and the economic model, c) lack of justification on zero disutility and/or costs assumptions.

a) According to the CS, the company modelled all Grade 3-4 AEs with at least a 2% difference in frequency between the interventions in the included trials, rather than the more common approach of including grade ≥3AEs that occur in at least 2% or 5% in either arm. The company's current approach implies that AEs with a high incidence in both arms (e.g., 80% and 81%) would not be included in the modelling. Although this approach lacks face-validity and may add uncertainty to the cost-effectiveness results, the EAG acknowledges that applying a different approach as a one-off cost and disutility likely has a limited impact. Nonetheless, a per cycle analysis (rather than assuming a one-off cost and disutility) including all Grade 3-4 AEs that occur in at least 2% of any arm would be reassuring to the EAG.
b) The EAG identified several inconsistencies between values related to AEs reported in the CS and the economic model. In the economic model a zero disutility and/or duration was assumed for several AEs while different values were reported in CS, Table 51. Likewise, for the costs of several AEs there was a mismatch between the values reported in CS, Table 64 and the economic model (i.e., costs were assumed to be zero in the economic model, contrary to the costs reported in CS, Table 64). In addition, not all AEs reported in CS, Table 49 were also present in CS, Tables 51 and 64. The EAG would like the company to further justify these inconsistencies and provide a correct economic model if deemed appropriate.
c) Tables 51 and 64 from the CS reported the AEs disutilities and costs applied in the economic model. However, the company did not provide sufficient justification for some of the values used, despite being asked in the clarification letter. More specifically, several AEs were assumed to have a zero disutility without appropriate justification, and for several AEs the duration and/or utility decrement were reported without justification or reference to their source. The lack of justification is especially concerning for AEs (e.g., thrombocytopenia) which had a non-negligible incidence according to the trials In response to the EAGs request to provide justifications for the AE disutility and costs assumptions in clarification question B14,[13] the company acknowledged the *"potentially arbitrary assumption within the model"* and mentioned that the same approach was applied in other TAs. Although the EAG

understands that economic modelling is inherent to making assumptions, these should be supported by evidence, either from relevant external data or expert opinion and hence the company should provide this.

4.2.8 Health-related quality of life (HRQoL)

Health state utility values were estimated for the progression-free and progressed health states. Selpercatinib HRQoL data were collected in the LIBRETTO-001 trial using the EORTC QLQ-C30 questionnaire. These were completed by patients prior to receiving the drug on the first day of the treatment, every second cycle in the first year, every third cycle from cycle 13, and at the post-discontinuation follow-up visit. Due to the lack of EQ-5D data from the LIBRETTO-001 study, the company explored various mapping techniques to map the collected EORTC QLQ-C30 data to EQ-5D-3L (CS, Table 50). The CS base-case implemented the EQ-5D-3L results from the algorithm outlined by Young et al 2015,[46] as it resulted in the lowest, and according to the company most plausible utility estimates (CS, Table 50).

As per the CS, most responses to treatment with selpercatinib reported in the LIBRETTO-001 trial were partial responses. The company assumed that it was unlikely that responders would have an important improvement in their HRQoL, and hence an adjustment to the progression-free utility weight to reflect response was not deemed necessary.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, Appendix H,[8] QoL data was not deemed necessary to be extracted from the economic SLR, as the utility values for the selpercatinib model were obtained from the LIBRETTO-001 trial and mapped to EQ-5D data using the algorithm presented in Young et al 2015.[46]

4.2.8.2 Health state utility values

A summary of all HSUVs used in the cost-effectiveness analysis is provided in Table 4.6. For the CS base-case, utility values were assumed to be treatment independent. Scenario analyses were performed to explore utility values from other relevant TAs (i.e., TA654 and TA812).

Table 4.6: Health state utility values

	Health state	Utility value	Reference
CS base-case	PF	[redacted]	LIBRETTO-001 mapped with Young et al 2015 algorithm
	PD	[redacted]	
CS scenario analysis	PF	[redacted]	TA654[47]
	PD	[redacted]	

Based on CS, Tables 52 and 53
CS = company submission; PD = progressive disease; PF = progression-free

4.2.8.3 Disutility values

Disutility values were applied to the AE incidence rates from the LIBRETTO-001 and KEYNOTE-189 trials (CS, Table 49) to capture the impact of AEs on HRQoL in the economic model. All AEs were assumed to occur in the first cycle of the model and last for a prespecified duration (CS, Table 51). Each AE had a specific utility decrement based on previous NICE TAs and company's assumptions.

EAG comment: The main concerns of the EAG relate to: a) high utility values compared with other TAs, and small decrement between PF and PD utility values, b) use of mapping algorithm.

a) Utility values to inform the company's base-case (PF = [redacted], PD = [redacted]) were higher than the ones used in other relevant TAs, and only slightly lower than the age and gender matched UK general population norm (0.819). Moreover, the decrement for disease progression ([redacted]) seems relatively small. The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers. Upon request, the company provided scenario analyses exploring utility values from other relevant TAs, resulted in higher ICERs (NMB not reported) ranging from £5,299 and £6,253 per QALY gained (original £5,264 per QALY gained) compared to pembrolizumab combination therapy and £36,046 to £41,985 per QALY gained (original £35,883 per QALY gained) compared to pemetrexed plus platinum chemotherapy. In response to clarification question B17b,[13] the company acknowledged that the number of completed post-progression HRQoL questionnaires was limited ([redacted] observations) and that this could potentially explain the relatively small utility decrement for progressed disease. The EAG agrees that the few HRQoL data informing PD utility were collected early after patients progressed and therefore may not capture the full impact of disease progression on HRQoL, which may have led to an overestimation of the PD utility. Therefore, the EAG preferred to inform their base-case using the PD utility (0.678) from TA654 (also accepted in TA812 for untreated patients with RET fusion-positive NSCLC), which resulted in ICERs of £5,599 and £42,187 per QALY gained when compared to pembrolizumab combination therapy and pemetrexed + platinum chemotherapy, respectively. Additionally, the EAG explored a scenario analysis with both PF (0.794) and PD utility values from TA654, which resulted in ICERs of £5,626 and £42,407 per QALY gained when compared to pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, respectively.[47]
b) The company mapped EORTC QLQ-C30 data to EQ-5D data to inform HSUVs, because EQ-5D data were not collected in the LIBRETTO-001 trial. After comparing four different mapping techniques the company chose the mapping algorithm outlined by Young et al 2015,[46] as it had the lowest, and supposedly most plausible estimates. As per NICE TSD 10[48], when EQ-5D instruments may not be available, a mapping function can be used, as long as it has been demonstrated and validated. Given the number of mapping algorithms available and the fact the Young et al 2015 algorithm was based on a population that included patients with multiple myeloma (n=572), breast cancer (n=100) and lung cancer (n=99)[46], the EAG would have expected further justification based on literature on the validity of the specific mapping algorithm for this population of NSCLC.

4.2.9 Resources and costs

The cost categories included in the model were drug acquisition costs, medical costs (treatment administration and monitoring, subsequent treatments, medical management of the condition by health state), costs of managing AEs, and end of life costs.

Unit prices were based on the NHS reference prices, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF), Eli Lilly and Company, electronic market information tool (eMIT), and past relevant NICE TAs.

4.2.9.1 Resource use and costs data identified in the review

According to the CS, modelled costs and resource use were based on the targeted literature review of relevant and previously accepted TAs by NICE for first line treatments in patients with advanced and/or metastatic NSCLC. Therefore, no further extraction of studies from the SLR to identify cost-effectiveness studies was performed.

4.2.9.2 Treatment costs

Drug acquisition costs of selpercatinib were provided by the company, while the costs for relevant comparators were based on their list price extracted from the BNF or eMIT as summarised in Table 4.7.

Drug acquisition costs were divided into treatment periods according to the dosing schedules of each treatment as summarised in Table 4.8. Costs for treatment cycle 1 were based on the planned dosing schedule, while in the subsequent treatment cycles costs were adjusted to reflect the mean dose intensity observed in the trials. For selpercatinib, treatment costs in the first 4 weeks (period 1, 28 days) with a mean dose of 293.33 mg and a price of [redacted] per mg was [redacted] (including PAS). Thereafter (period 2, week 4+), the treatment costs per cycle with a mean dose of 251.07 mg and a price [redacted] per mg was [redacted] (including PAS). For the pembrolizumab combination therapy arm, the cost was £6,449.76 for period 1 (weeks 0-2), £5,507.45 for period 2 (weeks 3-11), £5,491.98 for period 3 (week 12-103), and £994.68 for period 4 (week 104+). Treatment costs of pemetrexed plus platinum chemotherapy were £1,189.76 for period 1 (week 0-2), £1,010.15 for period (week 3-17), and £994.68 for period 3 (week 18+).

A mean body weight of 72.2 kg and a body surface area of 1.81 m^2 were used for adjusted dose interventions as sourced from TA520[49]. The weighted average cost was applied in the model for selpercatinib to account for dose reductions for toxicity control and weight-based dosing. A relative dose intensity (RDI) equivalent to selpercatinib from LIBRETTO-001 was applied to the comparators.

Drug wastage was also applied in the company's base case, assuming a whole tablet for oral drugs and the lowest cost of opened vials for the available sizes.

Table 4.7: Drug acquisition costs for selpercatinib and relevant comparators

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)
Selpercatinib				
Selpercatinib	Capsules	80 mg	60	[redacted][a]
Selpercatinib	Capsules	40 mg	60	[redacted][a]
Pembrolizumab plus pemetrexed plus carboplatin				
Pembrolizumab	Vial	25 mg/ml	4 ml	2,630.00[b]
Pemetrexed	Powder	100 mg	1 ml	128.00[b]
Carboplatin	Vial	10 mg/ml	15 ml	6.08[c]
Pemetrexed plus platinum chemotherapy				
Pemetrexed	Powder	100 mg	1 ml	128.00[b]
Carboplatin	Vial	10 mg/ml	15 ml	6.08[c]

Based on Table 54, CS.[3]
[b]BNF 2021[50]
[c]eMIT 2021[51]
[a] Cost including PAS discount

BNF = British National Formulary 2021; eMIT = electronic market information tool 2021; PAS = Patient Access Scheme

Table 4.8: Treatment costs included in cost-effectiveness model

Treatment	Cycle length		Period 1 cost (£)	Period 2 cost (£)	Period 3 cost (£)	Period 4 cost (£)
Selpercatinib		**Week**	**0-3**	**4+**	**-**	**-**
Selpercatinib	4 weeks		[redacted][a]	[redacted][a]	-	-
Pembrolizumab plus pemetrexed plus carboplatin		**Week**	**0-2**	**3-11**	**12-103**	**104+**
Pembrolizumab	3 weeks		5,260.00	4,497.30	4,497.30	0.00
Pemetrexed	3 weeks		1,172.27	994.68	994.68	994.68
Carboplatin	3 weeks		17.49	15.46	0.00	0.00
Total			6,449.76	5,507.45	5,491.98	994.68
Pemetrexed plus platinum chemotherapy		**Week**	**0-2**	**3-17**	**18+**	**-**
Pemetrexed	3 weeks		1,172.27	994.68	994.68	-
Carboplatin	3 weeks		17.49	15.46	0.00	-
Total			1,189.76	1,010.15	994.68	-

Based on NICE TA584;[71] Planchard et al 2018;[102] Langer et al 2016;[104] Doebele et al 2015. Based on CS model, costs tab.

[a] Cost including PAS discount

CS = company submission; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; TA = Technology Appraisal

4.2.9.3 Administration costs

Treatment administration and monitoring costs were based on NHS reference costs 2019/2020[52], PSSRU 2021[53], TA520[49] and TA557[54] and included 12 minutes of pharmacy time for selpercatinib, as summarized in Table 59 in the CS. During treatment with any of the three interventions, patients were assumed to have one oncologist visit every 3 weeks (consistent with TA520[49]). In addition, in alignment with the summary of product characteristics (SmPC), patients treated with selpercatinib received seven ECGs.

4.2.9.4 Subsequent treatments

The subsequent treatment distributions in the company's base-case were informed by previous NICE TAs[5,6,55] and their costs were applied at the time of disease progression as one-off cost as summarised in Table 4.9. Subsequent treatment distributions provided by the expert oncologist were used in a scenario analysis to explore their impact on the cost-effectiveness estimates.

Subsequent treatment costs included the time on treatment, associated administration costs, and the fraction of patients receiving each post-progression therapy.

Table 4.9: Subsequent treatment distributions and costs applied in the base-case analysis

Treatment	Mean cost (£)	Selpercatinib (%)	Pembrolizumab plus pemetrexed plus carboplatin/cisplatin (%)	Pemetrexed plus carboplatin/cisplatin (%)
Docetaxel	1,419	55%	100%	15%
Nivolumab	13,536	0%	0%	34%
Pembrolizumab	30,984	0%	0%	34%
Atezolizumab	16,351	0%	0%	17%
Carboplatin	1,437	0%	0%	0%
Docetaxel plus nintedanib	9,998	0%	0%	0%
Pemetrexed plus carboplatin	8,110	45%	0%	0%
BSC	9,894	0%	0%	0%
Total (one-off) costs		4,430.00	1,419.00	18,130.00

Based on CS model, costs tab and CS Table 60.[3]
BSC = best supportive care; CS = company submission

4.2.9.5 Health state costs

Health state resource use estimates were based on TA654[47] for osimertinib (CS, Table 62), which the company considered a reasonable proxy. The mean (weekly) cycle costs per for progression-free state was £74.79, whilst the per cycle costs for progressed disease was £118,10. A scenario analysis was performed in which resource use estimates were based on an expert oncologist (CS, Table 63).

4.2.9.6 Adverse event costs

Adverse event costs were calculated based on the incidence rates presented in Table 51 in the CS and applied as a one-off cost in the first model cycle. All AEs were assumed to last for a single cycle in line with previous cost-effectiveness analyses in NSCLC.

4.2.9.7 End-of-life costs

A one-off end of life cost of £4,189.76, which included hospital admission and excess bed days, Macmillan nurse home visits and hospice care stays, was included in the second line setting based on costs reported in NICE TA654.[47]

4.2.9.8 Miscellaneous unit costs

Despite the company's belief that no costs for genetic testing should be included in the analysis, a cost of £34 per tested patient was included in the company's base case as reported in NICE TA760.[42]

EAG comment:

- The main concerns of the EAG relate to a) the company's choices for the modelling of subsequent treatments, and b) errors in the economic model related to subsequent treatments.

  a) The EAG questions the company's base-case subsequent treatment distribution. The distribution of subsequent treatments in the company's base-case was informed by prior NICE TAs in NSCLC, and a scenario analysis was conducted in which subsequent treatments were informed by an expert oncologist. In response to the clarification letter, the company explained

that the subsequent treatment distribution based on previous immunotherapy appraisals was deemed more appropriate given immunotherapy (pembrolizumab combination therapy) was a main comparator for this appraisal. The EAG, however, questions the plausibility of the company's base-case approach, as it does not align with the care pathway for RET fusion-positive advanced NSCLC in NG122. According to NG122, after first line pembrolizumab combination therapy patients (regardless of their PD-L1 status) should be treated with either docetaxel as a monotherapy or in combination with nintendanib, or selpercatinib. After first line pemetrexed plus platinum chemotherapy, the NG122 recommends pembrolizumab, atezolizumab, nivolumab, docetaxel plus nintendanib and selpercatinib as subsequent treatment option. In contrast, in the company's base-case 100% of patients in the pembrolizumab combination therapy arm are assumed to receive subsequent docetaxel monotherapy and docetaxel and nintendanib combination therapy was not part of the subsequent treatment distribution for patients after pemetrexed plus platinum chemotherapy. Although selpercatinib would also be a subsequent treatment option according to NG122, the EAG agrees that second line selpercatinib should be excluded as it is currently in the CDF, as pointed out by the company in response to clarification question B21c. For the subsequent treatment distribution post selpercatinib, the company stated that estimates were based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. Considering the targeted treatments in NG122, it is unclear to the EAG how the company in the end modelled patients to receive docetaxel monotherapy and pemetrexed plus platinum chemotherapy post selpercatinib and further justification for this is necessary. In addition, although the expert oncologist expected a substantial proportion of patients to receive BSC as a subsequent treatment, it was not considered as an option in the company's base-case and the company acknowledged this to be a potential limitation in response to clarification question B21b.

In the EAG base-case, subsequent therapies after pembrolizumab combination therapy were modelled in line with NG122 and the footnote below CS, Table 61, i.e., 15% docetaxel, 50% docetaxel plus nintendanib and 35% BSC. After pemetrexed plus platinum chemotherapy, patients in the EAG base-case were modelled in line with NG122 and the values of the expert oncologist as reported in CS, Table 61. As the EAG considered the company's justification for the modelling of subsequent treatments after selpercatinib to be insufficient and it is currently unclear which subsequent treatment options would be appropriate after first line selpercatinib (given that it is currently not part of the clinical care pathway as a first-line option), the EAG would ideally inform subsequent treatments post selpercatinib based on data from the LIBRETTO-001 trial. Although the company provided these data in Table 32 of the clarification response, it was not possible for the EAG to implement these into the economic model and this analysis should therefore be explored by the company in a scenario analysis. As an alternative, the EAG, in its base-case, modelled subsequent treatments post selpercatinib in line with the expert oncologist values as reported in CS, Table 61. Given that the company did not include pembrolizumab combination therapy as a subsequent treatment option after selpercatinib in its economic model, the EAG slightly amended the expert oncologist values and modelled 5% of patients to receive subsequent atezolizumab/pembrolizumab, 75% pemetrexed plus platinum chemotherapy and 20% BSC.

b) The EAG identified two errors in the economic model related to the modelling of subsequent treatments. First, CS, Table 60 and the clinical validation meeting minutes report that in the company's base-case patients after selpercatinib are assumed to receive docetaxel or pemetrexed plus platinum chemotherapy. However, in the economic model patients received carboplatin monotherapy rather than pemetrexed plus platinum chemotherapy, which favoured the selpercatinib arm. The EAG corrected this error and modelled subsequent treatments after

selpercatinib in line with CS, Table 60 and the clinical validation minutes. Second, the EAG identified an error in the calculation of total subsequent treatment costs in all arms: the subsequent treatment costs of docetaxel plus nintendanib, pemetrexed plus platinum chemotherapy, and BSC were not included in the total subsequent treatment costs calculation. The EAG corrected this error to make sure all subsequent treatment options in the model were part of the total subsequent treatment costs calculation. The company's deterministic base-case after correcting for the two errors resulted in an incremental cost-effectiveness ratio (ICER) of £36,909 per quality adjusted life year (QALY) gained (NMB -£2,380) versus pemetrexed plus platinum chemotherapy and £6,551 per QALY gained (NMB £61,500) versus pembrolizumab combination therapy.

4.2.10 Severity

The company used the severity modifier tool developed by ScHARR and Lumanity to calculate the absolute and proportional severity modifiers (CS, Table 66). The company stated that, in line with the NICE reference case, the Hernandez-Alava 2017 study was used to inform the base-case analysis and a number of other sources were explored in scenarios (CS, Table 67). All analyses resulted in a QALY modifier of 1.2, which the company applied to the willingness-to-pay (WTP) threshold (£36,000 per QALY) in its base-case.

EAG comment: The EAG reproduced the shortfall analysis reported in CS Section B.3.5. The reported absolute and proportional QALY shortfall (CS, Table 67) and the 1.2 x QALY weight were successfully reproduced.

5. COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

The CS base-case cost-effectiveness results (probabilistic) indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively amounting to ICERs of £36,025 and £5,209 per QALY gained (CS, Table 71 and Table 5.1 below). The NHB for the probabilistic analyses was not reported in the CS, thus these were calculated by the EAG to be [redacted] and [redacted] for selpercatinib versus pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (with a severity modifier of 1.2 on the QALY, i.e., a WTP threshold of £36,000 per QALY). Consequently, pemetrexed plus platinum chemotherapy with pembrolizumab was extendedly dominated. The probability of selpercatinib being cost-effective, at threshold values of £30,000 and £40,000 per QALY gained were estimated to be [redacted] (CS, Figure 31).

Table 5.1: Probabilistic CS base-case results

Intervention	QALYs	Costs (£)	Incremental QALYs	Incremental Costs	Incremental ICER (£/QALY)
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
Pembrolizumab plus pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Selpercatinib	[redacted]	[redacted]			36,025

Source: Table 71, CS.[3]
CS = company submission; ICERs = incremental cost-effectiveness ratios; QALYs = quality-adjusted life years

Overall, the technology is modelled to affect QALYs by:

- Increased PFS for selpercatinib (QALYs in the progression-free (PF) health state increased by [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and increased OS for selpercatinib (survival (undiscounted) increased by 4.110 and 3.361 years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). This resulted in post-progression benefits of [redacted] and [redacted] QALYs compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (estimates retrieved from CS, Appendix J).
- Treatment benefit (in terms of OS and PFS) are maintained for the whole duration of the time horizon i.e., no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and higher disease management costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). These costs are partly offset by lower subsequent treatment costs (cost

savings of [redacted] and [redacted]compared with pemetrexed + platinum chemotherapy and pembrolizumab combination therapy respectively; estimates retrieved from CS, Appendix J).

EAG comment:

- The main concerns of the EAG relate to the extent and plausibility of the observed gains accumulated beyond the observed data period. In clarification question B23, the EAG requested the company to provide a comparison of the observed (progression-free) survival for instance using restricted mean survival time (RMST) and the undiscounted life years (LYs) as well as undiscounted progression-free LY (PFLY) estimated based on the economic model and elaborate on the plausibility of the differences. Unfortunately, the company did not provide the estimated proportion of gains accumulated beyond the observed data period for the increment. Therefore, the EAG calculated these proportions of gains accumulated beyond the observed data period (note that numbers might be subject to rounding errors). Based on clarification response Table 31 the following statements can be made:
    - The proportion of (PF)LY accumulated beyond the observed data is [redacted] for selpercatinib than for pemetrexed plus platinum chemotherapy.
    - The observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon.
    - Considering the increments, approximately [redacted] (or more depending on the truncation point) of the LYs are gained beyond the observed data period for selpercatinib compared with pemetrexed plus platinum chemotherapy while this is approximately [redacted] (or more depending on the truncation point) for PFLY.
- These findings indicate that the large majority of (PF)LY gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B23). This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2).
- In addition to the above, it is noticeable that the observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated (see Section 4.2.6).

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's DSAs) were:

- Discount rate for costs
- Discount rate for outcomes
- Drug administration costs
- Subsequent active systemic anticancer therapy costs
- Drug related monitoring costs
- AE costs

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the ICER were related to:

- Estimation of TTD
- Estimation of PFS
- Estimation of OS
- Subsequent therapy distribution
- Assuming alternative utility values (from TA654)

EAG comment:

- The main concerns of the EAG relate to a) the runtime of the probabilistic analyses and b) counterintuitive deterministic sensitivity analyses results (CS, Figures 32 and 33).

  a) The PSA requires a relatively long run time (as also mentioned in CS, Section B.3.10.3) which hampers the EAG to perform analyses. Unfortunately, according to the company, there are no straightforward adjustments that were found to speed up the run time of the probabilistic analyses (response to clarification question B28).
  b) The CS, Figures 32 and 33 (tornado diagram) included counterintuitive results (which was due to an error as indicated in response to clarification question B27). The company provided corrected tornado diagrams, see clarification response B27 (Figure 20 and Figure 21).

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC. The company noted that considering the currently immature OS data available from the LIBRETTO-001 trial, a thorough clinical validation process was conducted in order to inform survival analysis for the OS extrapolations selected for the base case analysis. Moreover, the company stated that clinical feedback was also used to validate the resource use inputs utilised in the model, including subsequent treatment choices and monitoring frequencies.

5.3.2 Technical verification

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

5.3.3 Comparisons with other technology appraisals

No comparisons with other TAs were reported in CS, Section B.3.13 (reporting on validation). However, the company stated that where possible, UK sources were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted. This includes the adoption of the cohort-based partitioned survival model approach, in line with a number of prior NICE appraisals in

NSCLC, including TA683[21], TA705[7] and TA760[42]. Moreover, CS, Table 36 provides and overview of features of the economic analysis compared with TA654[47], TA683[21], TA760[42] and TA812.[56]

5.3.4 Comparison with external data used to develop the economic model

According to the company, it was not possible to conduct external validation of model outcomes for selpercatinib against trial data as the median PFS and OS were not yet reached in the LIBRETTO-001 trial for the SAS1 population.

5.3.5 Comparison with external data not used to develop the economic model

Clinical feedback was used to validate the curve choices to extrapolate the trial data over the lifetime time horizon of the model. In addition, model estimates for median PFS and OS for selpercatinib were consistent with real-world data obtained in RET fusion-positive NSCLC patients receiving selective tyrosine kinase inhibitor (TKI) in clinical practice (CS, Table 73). Model estimates for median PFS and OS for both pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy were also found to be consistent with estimates obtained during the phase III KEYNOTE trial in untreated, metastatic non-squamous NSCLC patients (CS, Table 73).

EAG comment: The main concerns of the EAG relate to the technical verification provided by the company. The EAG asked to company to complete the TECH-VER checklist to support the technical verification of the economic model (clarification question B27). This was not provided by the company. According to the company the checklist used by the company was derived based on the TECH-VER checklist and thus provided the same verification of validity as the TECH-VER checklist. This seems reasonable to the EAG (though the EAG is unable to verify this as the company's checklist was not provided in response to clarification question B27).

6. EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost-effectiveness categorised according to the sources of uncertainty as defined by Grimm et al 2020[57]:

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost-effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al 2016[58]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong).
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Subsequent treatment costs of docetaxel plus nintendanib, pemetrexed plus platinum chemotherapy, and BSC were not included in the total subsequent treatment costs calculation (Section 4.2.9).
   The error was corrected by including all subsequent treatment options in the model to the total subsequent treatment costs calculation.
2. Inconsistency in subsequent treatment distribution after selpercatinib between the CS/clinical validation minutes (docetaxel or pemetrexed plus platinum chemotherapy) and the economic model (docetaxel or carboplatin monotherapy) (Section 4.2.9).

The error was corrected by modelling subsequent treatments after selpercatinib in line with the CS and the clinical validation minutes.

6.1.1.2 Fixing violations

No FVs were identified by the EAG.

6.1.1.3 Matters of judgement

3. Progressed disease utility based on TA654 (Section 4.2.8).
   The progressed disease utility from TA654 was used instead of the progressed disease utility informed by the LIBRETTO-001 trial.
4. Subsequent treatment distribution and values based on NG122 and expert oncologist inputs (Section 4.2.9).
   Subsequent treatment distribution and values for all arms were based on NG122 and expert oncologist inputs instead of based on previous immunotherapy appraisals.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Scenario analyses – impact of data immaturity and lack of transparency

To reflect the uncertainty due to data immaturity, and resulting ambiguity in choice of survival curves, the EAG conducted scenario analyses to find the range of results given plausible parametric survival curves. To do so, a set of plausible scenarios was defined and results of the most and least beneficial plausible survival curves for OS and PFS for each comparator individually were reported.

Plausibility was defined by:

a) Being closer to an expert estimate or external source than the curve chosen by the company.
b) The curve having a plausible shape.

For both comparators, the lognormal curves were excluded as they produced clinically implausible tails with almost 8% and 2% patients surviving at 10 and 20 years. Further, in the pemetrexed plus platinum chemotherapy comparison, the spline knot 3 curve was excluded for PFS, as the curve had an implausible shape (PFS increasing).

Based on this, for the comparison with pembrolizumab combination therapy, the exponential, and Gompertz curves were considered for PFS and the exponential, spline knot 2 and stratified Gompertz curves were considered for OS. For the comparison with pemetrexed plus platinum chemotherapy, the exponential, and Gompertz curves were considered for PFS and the stratified lognormal, lognormal, exponential, loglogistic, spline knot 2 and stratified Gompertz curves were considered for OS.

Please note that there was a mismatch between the modelled PFS, and OS values as reported in the CS and the actual values used in the economic model (see Section 4.2.6. critique b) d.). The EAG scenario analyses to explore the impact of data immaturity and lack of transparency were conducted based on the values reported in the CS. The following are the exploratory scenario analyses:

5. Survival curves with highest NMB (Section 4.2.6).
   The EAG selected the exponential curve for PFS and OS in both arms.
6. Survival curves with lowest NMB (Section 4.2.6).
   The EAG selected the Gompertz curve for PFS in both arms and the stratified Gompertz curve for OS in both arms.

7. Progression-free and progressed disease utility based on TA654 (Section 4.2.8).
   The EAG selected the progression-free and progressed disease utilities from TA654 instead of the progression-free and progressed disease utilities informed by the LIBRETTO-001 trial.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost-effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period	4.2.2	Methods	Compare results of PSM to the outcomes of a STM	+/-	No	Use of STM to assist in verifying the plausibility of PSM extrapolations
The data obtained from the LIBRETTO-001 trial for OS and PFS is immature, adding substantial uncertainty to the extrapolated survival data in the economic model	4.2.6	Imprecision	Scenario analyses to find range of results given plausible parametric survival curves	+/-	No	Long-term PFS and OS data to reduce the uncertainty around the cost-effectiveness results
The company's choice of survival curves for the modelling of treatment effectiveness was not transparent	4.2.6	Transparency	More details concerning the choice of parametric survival curves	+/-	No	More information about a) the choice of considering complex survival curves, b) plots not provided in the clarification response c) the choice between survival curves in detail and d) the mismatch between reported PFS and OS values in the CS and the economic model
No treatment waning was explored	4.2.6	Bias and indirectness	Hazard ratio plots for PFS and OS versus time	+/-	No	Hazard ratio plots for PFS and OS versus time. Scenario analyses to explore the impact of

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
			Scenario analyses to explore the impact of treatment waning into the model			treatment waning into the model
The observed PFS for pemetrexed plus platinum chemotherapy is larger than the modelled PFS. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated	4.2.6 and 5.1	Bias and indirectness	Alternative approaches to estimate PFS for pemetrexed + platinum chemotherapy where the modelled PFS > observed PFS for pemetrexed + platinum chemotherapy	+	No	Long-term PFS data.
Utility values in the company's base-case were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states	4.2.8	Bias and indirectness	Scenario analyses exploring utility values from other relevant TAs. PD utility from TA654	+	Yes	N/A

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
The plausibility of the company's choices for the modelling of subsequent treatments	4.2.9	Methods	Informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Informing subsequent treatments for the comparators based on NG122 and expert oncologist input	+/-	Partly	A scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator

[b] Explored

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PSM = partitioned survival model; STM = state transition model; TAs = Technology Appraisals; UK = United Kingdom

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
CS base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (1-Error in calculation of total subsequent treatment costs)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (2-Inconsistency subsequent treatment after selpercatinib)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,662	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,987	[redacted]	[redacted]
Matter of judgement (3-PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,478	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,859	[redacted]	[redacted]
Matter of judgement (4-Subsequent treatments based on NG122 and expert oncologist)							
Selpercatinib	[redacted]	[redacted]					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,467	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,347	[redacted]	[redacted]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,230	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,535	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for WTP of £36,000 per QALY

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NG122 = NICE guideline 122; PD = progressed disease; QALY = quality adjusted life year; TA = Technology Appraisal; WTP = willingness-to-pay

Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Scenario analysis (5-Survival curves with highest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,970	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,442	[redacted]	[redacted]
Scenario analysis (6-Survival curves with lowest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£60,969	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	-£6,963	[redacted]	[redacted]
Scenario analysis (7-PF and PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,407	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,626	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for WTP of £36,000 per QALY

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NMB = net monetary benefit; PF = progression-free; PD = progressed disease; QALY = quality adjusted life year; TA = technology appraisal; WTP = willingness-to-pay

6.3 EAG's preferred assumptions

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, were £42,230 and £5,535 per QALY gained for selpercatinib versus pemetrexed plus platinum chemotherapy and the pembrolizumab combination therapy respectively. The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of 0.0% and 1.5% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NG122 and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

6.4 Conclusions of the cost-effectiveness section

The company's cost-effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the lack of systematic reviews to identify HRQoL and resource use and costs studies, and it was unclear to the EAG whether the UK tariff was used to value HRQoL. The most prominent issues highlighted by the EAG were: 1) the lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period, 2) immaturity of PFS and OS data from the LIBRETTO-001 trial, adding substantial uncertainty to the extrapolated survival data in the economic model, 3) the lack of transparency in the company's choice of survival curves, 4) the lack of exploring potential waning of the selpercatinib treatment effect, 5) the use of relatively high utility values with a small progressed disease decrement, 6) the plausibility of the

modelled subsequent treatments in the company's base-case, and 7) potential underestimation of the modelled PFS in the pemetrexed plus platinum chemotherapy arm.

First, the EAG was concerned about the lack of a STM to verify the plausibility of the company's PSM extrapolations and to explore key clinical uncertainties in the extrapolation period as recommended by NICE DSU TSD19. The PFS and OS data for selpercatinib from LIBRETTO-001 were relatively immature, and the large majority of modelled (PF)LY gains were accumulated beyond the observed data period. Hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted. To assist in verifying the plausibility of the partitioned survival model extrapolations, the EAG would like to see the outcomes of a state transition model.

Second, the relatively immature data from the LIBRETTO-001 trial informing the PFS and OS of selpercatinib added substantial uncertainty to the extrapolated survival data in the economic model. In addition to the company's scenario analyses in the CS, the EAG conducted scenario analyses to explore a range of plausible PFS and OS curves. These scenario analyses resulted in a wide range of NMBs, confirming the substantial uncertainty surrounding the extrapolated survival data.

Third, the EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent. It was unclear to the EAG why the company selected a spline model for the modelling of OS rather than a standard parametric model, and the company did not provide plots of the standard normal quartiles versus log time and log survival odds versus log time to examine the diagnostics of the parametric survival models based on the observed data. In addition, although the company preferred expert inputs over statistical and visual fit of the parametric survival curves to the KM data to inform the choice of survival curve, it was unclear to the EAG why the company did not always select the curve closest to the expert inputs. Next to that, the modelled PFS and OS values as reported in the CS did not match with the values informing PFS and OS in the economic model for several survival curves, including the company's base-case. These transparency issues, in addition to the immaturity of the LIBRETTO-001 trial data, add substantial uncertainty to the extrapolated PFS, OS, and TTD.

Fourth, the company assumed that there was no waning of the selpercatinib treatment effect in its base-case. The company stated that there was no evidence of relative treatment waning in the single-arm LIBRETTO-001 trial for selpercatinib. The EAG requested further justification as to why no treatment waning was considered and requested hazard ratio plots for PFS and OS versus time for both comparisons (not provided), as well as an updated economic model and scenario analyses exploring treatment waning kicking in at different time points (not provided). The EAG would like to stress that these analyses are important for the assessment of the potential impact of treatment waning on the cost-effectiveness results, especially given that the current PFS and OS data are immature.

Fifth, utility values to inform the company's base-case (PF = [redacted], PD = [redacted]) were higher than the ones used in other relevant TAs, and only slightly lower than the age and gender matched UK general population norm (0.819). Moreover, the decrement for disease progression ([redacted]) seems relatively small. The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers. The number of completed post-progression HRQoL questionnaires to inform PD utility was limited ([redacted] observations) and data were collected early after patients progressed, which may have led to an overestimation of the PD utility. Therefore, the EAG preferred to inform their base-case using the PD utility (0.678) from TA654. Additionally, the EAG explored a scenario analysis with both PF (0.794) and PD utility values from TA654.

Sixth, the distribution of subsequent treatments in the company's base-case was informed by prior NICE TAs in NSCLC. The EAG, however, questions the plausibility of the company's base-case approach, as it does not align with the care pathway for RET fusion-positive advanced NSCLC in NG122. Several second-line subsequent treatment options in NG122 for patients in the comparator arms were not modelled in the company's base-case. Subsequent treatments post selpercatinib were based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. Considering the targeted treatments in NG122, it was unclear to the EAG why the company in the end modelled patients to receive docetaxel monotherapy and pemetrexed plus platinum chemotherapy post selpercatinib and further justification for this is necessary. In addition, although the expert oncologist expected a substantial proportion of patients to receive BSC as a subsequent treatment, it was not considered as an option in the company's base-case. Therefore, the EAG in its base-case modelled subsequent treatments for the comparators in line with NG122 and expert oncologist inputs (CS, Table 61). The EAG would ideally inform subsequent treatments post selpercatinib based on data from the LIBRETTO-001 trial, and although the company provided these data, it was not possible for the EAG to implement these into the economic model. As an alternative, the EAG modelled subsequent treatments post selpercatinib in line with the expert oncologist values.

Finally, the EAG was concerned that the modelled PFS in the pemetrexed plus platinum chemotherapy arm is potentially underestimated. Clarification response Table 31 showed that the observed PFS for pemetrexed plus platinum chemotherapy was larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy was underestimated and hence the increments versus selpercatinib potentially overestimated.

The CS base-case probabilistic ICERs versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy were £5,209 and £36,025 per QALY gained, respectively. The estimated EAG base-case ICERs (probabilistic) versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, based on the EAG preferred assumptions highlighted in Section 6.1, were £5,535 and £42,230 per QALY gained, respectively. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NG122 and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

In conclusion, there is large remaining uncertainty about the effectiveness and cost-effectiveness of selpercatinib, which can be partly resolved by the company by conducting further analyses. This includes providing outcomes of a STM to assist in verifying the plausibility of the PSM extrapolations, more transparency/details concerning the choice of parametric survival curves, scenario analyses exploring potential waning of the selpercatinib treatment effect, and a scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Mature long-term selpercatinib PFS and OS data would help to reduce the uncertainty surrounding the extrapolated survival data. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of selpercatinib compared with relevant comparators.

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