NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from **Roche**
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
5. **Evidence Review Group – factual accuracy check**
6. **Technical engagement response** from the company, **Roche**
7. **Technical engagement responses & expert statements from experts:**
   a. Professor Sanjay Popat, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group
8. **Technical engagement response from consultees and commentators:**
   a. Eli Lilly
9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
   a. Main critique
   b. Addendum

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID3875: Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer

Document B

Company evidence submission

August 2021

File name	Version	Contains confidential information	Date
ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_Document B_ACIC	1.0	Yes	12 August 2021

Contents

Tables and figures

Abbreviations

ADR	Adverse drug reaction
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATE	Average treatment effect
ATT	Average treatment effect in the treated
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BOIN	Bayesian optimal interval
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CBR	Clinical benefit rate
CCOD	Clinical cut-off date
CDF	Cancer Drugs Fund
CHMP	Committee for
CNS	Central nervous system
CPK	Creatinine phosphokinase
CRF	Case report form
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End-of-treatment

EQ-5D	EuroQol 5 Dimensions
ESS	Effective sample size
FIH	First in human
FISH	fluorescent in-situ hybridisation
FMI	Foundation Medicine
GLH	Genomic laboratory hub
GMS	Genomic Medicine Service
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ITT	Intention-to-treat
LYG	Life years gained
MAIC	Matching adjusted indirect comparison
MDP	Measurable Disease Population
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NGS	Next generation sequencing
NHSE	NHS England
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PBC	Platinum-based chemotherapy
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RANO	Response assessment in neuro-oncology
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
SAE	Serious adverse event
SLR	Systematic literature review

SOC	Standard of care
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event
TTD	Time to discontinuation
TTOT	Time-to-off treatment
ULN	Upper limit of normal
WBC	White blood cell

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, i.e. [redacted]

It should be noted that the focus of the current appraisal is the untreated population, given the unmet need for targeted treatment among *RET* fusion-positive NSCLC patients and the benefits that earlier targeted treatment would offer to these patients. However, in accordance with the anticipated indication, evidence for the population pre-treated with systemic regimens is also provided in this submission.

B.1.1.1 Rationale for selected comparators

Thirty-five comparators were included in the final scope for this appraisal, including all treatments available in the (treated and untreated) advanced NSCLC treatment pathway for both squamous and non-squamous patients. As comparators for this appraisal should reflect the current standard of care for *RET* fusion-positive patients in the NICE treatment pathway, including patients with both confirmed and unconfirmed *RET* fusion-positive status, Roche sought to identify the treatments that can be considered the current standard of care for these patients in UK clinical practice.

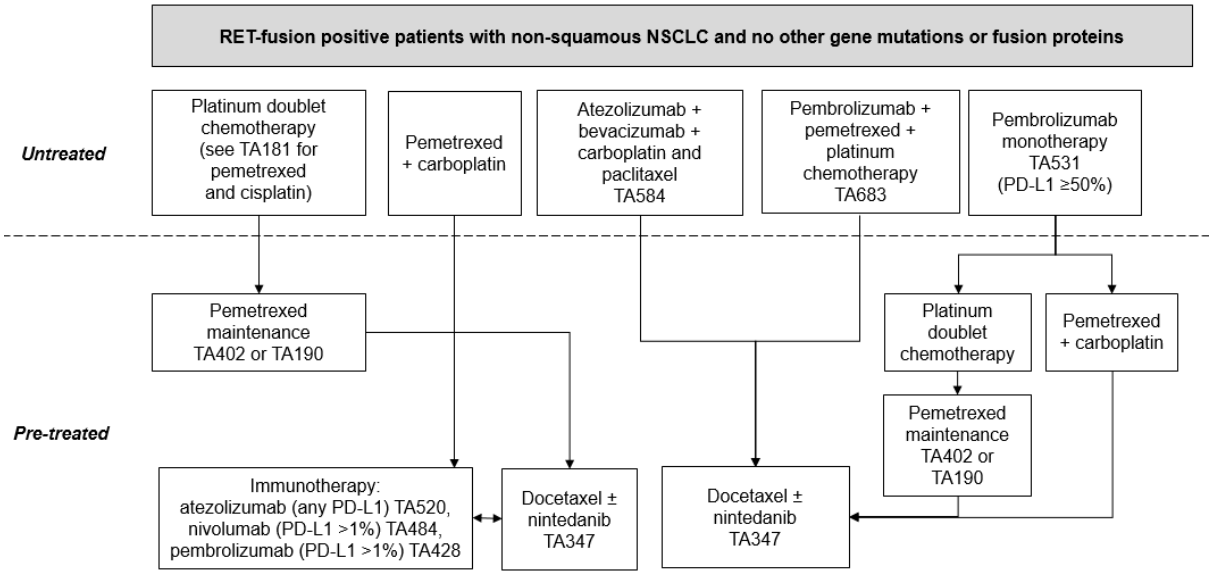
A high proportion of *RET* fusion-positive patients are non-squamous (1.4% of patients enrolled in ARROW were squamous NSCLC). Furthermore, *RET* fusion-positive patients tend to be younger, have never smoked and have Eastern Cooperative Oncology Group Performance Scores (ECOG PS) of 0–1 compared to wild type NSCLC patients (2).

After discussions with NICE at the Decision Problem Meeting (19 April 2021), it was agreed that due to the expected marketing authorisation for pralsetinib being line agnostic, separate treatment comparisons and cost-effectiveness analyses should be conducted for untreated and pre-treated (consisting of all treatments second-line and beyond) patients. These correspond with the treatment naïve and prior systemic treatment subgroups in ARROW. Therefore, comparators were separated into untreated and pre-treated treatments.

Roche conducted an advisory board with six leading UK NSCLC clinical experts in order to determine standard of care for *RET* fusion-positive patients and inform the comparator

choice for this appraisal (3). Due to the low incidence of *RET* fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore this appraisal is concentrated solely on non-squamous NSCLC patients, with the focus being the untreated population. Clinicians were therefore asked to determine the current standard of care for *RET* fusion-positive patients or patients who were not confirmed to be *RET* fusion-positive but had the typical characteristics of these patients (non-squamous, younger, never smoked and ECOG PS 0-1) from NICE's non-squamous treatment pathway (Figure 1).

Figure 1: NICE treatment pathway for non-squamous advanced NSCLC



NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1

Table 1 and Table 2 display the non-squamous untreated and pre-treated comparators suggested by NICE in the final scope, with justifications for their inclusion or exclusion in the current appraisal.

Table 1: Untreated comparators suggested in the final scope and justification for inclusion and exclusion in this appraisal

Treatment regimen	Population	Inclusion as comparator	Justification
Pembrolizumab + pemetrexed + chemotherapy	Non-squamous regardless of PD-L1 tumour expression	Yes	Widely used as standard of care for *RET* fusion-positive patients
Nivolumab + ipilimumab		No	Clinical experts at an advisory board suggested that this was not anticipated to be a widely used treatment option for *RET* fusion-positive patients
Pembrolizumab monotherapy		Yes	Widely used as standard of care for PD-L1≥50% treatment pathway. Clinical

	Non-squamous with PD-L1 ≥50%		experts in an advisory board meeting suggested that although this was widely used nationally by clinicians, immunotherapy is not an effective treatment for treating *RET* fusion-positive patients.
Atezolizumab monotherapy		No	Not anticipated to be a widely used treatment option for *RET* fusion-positive patients as stated by clinicians in an advisory board
Atezolizumab + bevacizumab + carboplatin + paclitaxel	Non-squamous with PD-L1 <50%	No	Not anticipated to be a widely used treatment option for *RET* fusion-positive patients as stated by clinicians in an advisory board
Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance	Non-squamous with PD-L1 <50% and adenocarcinoma or large cell carcinoma whose tumours express PD-L1 < 50%	No	Not anticipated to be a widely used treatment option for *RET* fusion-positive patients as stated by clinicians in an advisory board. Clinical experts suggested that platinum-doublet chemotherapy is a commonly used treatment option for wild type NSCLC patients. However, *RET* fusion-positive patients primarily consist of patients with an ECOG PS score of 0–1. Patients with these characteristics are unlikely to receive platinum-doublet chemotherapy in first-line and therefore, clinical experts advised not to include this as a comparator in the current NICE submission

ECOG PS, Eastern Cooperative Oncology Group Performance Score; NICE, National Institute for Health and Care Excellence, NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection

Table 2: Pre-treated comparators suggested in the final scope and justification for inclusion and exclusion in this appraisal

Treatment regimen	Population	Inclusion as comparator	Justification
Selpercatinib	*RET* fusion-positive	No	In the ongoing selpercatinib appraisal (ID3743), the company have actively pursued for the treatment to be available on the Cancer Drugs Fund. As treatments on the Cancer Drugs Fund are not eligible to be comparators in NICE submissions, selpercatinib has been omitted from comparison in this appraisal
Docetaxel with or without nintedanib	Non-squamous regardless of PD-L1 tumour expression	Yes	Widely used as standard of care for *RET* fusion-positive patients following treatment with pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy

Best supportive care		No	Given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate, or are willing to have pharmacological intervention will be eligible for pralsetinib, hence, BSC is not an appropriate comparator for this appraisal
Platinum doublet chemotherapy	Non-squamous with PD-L1 ≥ 50%	Yes	Widely used as standard of care for *RET* fusion-positive patients following treatment with pembrolizumab monotherapy. The treatment pathway (Figure 1) suggests that this treatment option may be followed by pemetrexed maintenance. Following consultation with clinical experts at an advisory board, advice was given to the company that pemetrexed is provided from the start of the treatment regimen alongside platinum doublet chemotherapy
Pemetrexed + carboplatin		Yes	Following advice with clinical experts at an advisory board, it was decided pemetrexed + carboplatin could be combined with the above regimen due to similarities between the treatment regimens
Atezolizumab monotherapy	Non-squamous with PD-L1 < 50%	No	Clinical experts at an advisory board suggested that this was not a widely used treatment option for *RET* fusion-positive patients due to the small number of *RET* fusion-positive patients in this treatment pathway following treatment with pemetrexed + carboplatin
Atezolizumab + bevacizumab + carboplatin + paclitaxel		No	Clinical experts at an advisory board suggested that this was not a widely used treatment option for *RET* fusion-positive patients due to the small number of *RET* fusion-positive patients in this treatment pathway
Pembrolizumab monotherapy		No	Clinical experts at an advisory board suggested that this was not a widely used treatment option for *RET* fusion-positive patients due to the small number of *RET* fusion-positive patients in this treatment pathway following treatment with pemetrexed + carboplatin

BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Score; NICE, National Institute for Health and Care Excellence, NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; *RET*, rearranged during transfection

Therefore, the comparators used in this appraisal are:

- Untreated:

    - Pembrolizumab + pemetrexed + chemotherapy (primary)
    - Pembrolizumab monotherapy (for patients in the PD-L1 ≥50% treatment pathway)
- Pre-treated:
    - Docetaxel monotherapy (primary)
    - Docetaxel + nintedanib
    - Platinum-based chemotherapy +/- pemetrexed (for patients in the PD-L1 ≥50% treatment pathway).

For the untreated population, pembrolizumab + pemetrexed + chemotherapy is listed as the primary comparator as per clinical expert guidance. For the pre-treated population, it should be noted that comparators align with the committee's recommendations in ID3743 where docetaxel monotherapy was the committee's preference as the primary comparator with docetaxel + nintedanib being recommended as a secondary comparator. In addition in this appraisal, the combination of platinum doublet chemotherapy and pemetrexed + carboplatin have been provided as one comparator (platinum-based chemotherapy +/- pemetrexed) as per clinical expert recommendation.

Table 3: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Pralsetinib	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	**Untreated disease:** For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab monotherapy (subject to ongoing appraisal ID1678) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) 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)	See description above and summary in Table 1 and Table 2	See description above and summary in Table 1 and Table 2

	• with or without pemetrexed maintenance treatment • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) • with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Atezolizumab monotherapy (subject to ongoing appraisal ID1678) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)		

	• Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) **For previously treated disease:** For people with RET fusion-positive NSCLC: • Selpercatinib (subject to ongoing appraisal ID3743) For people with non-squamous NSCLC PD-L1 ≥50%: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care For people with non-squamous NSCLC PD-L1 <50%: • Atezolizumab monotherapy • Atezolizumab with bevacizumab, carboplatin, and paclitaxel (only after failed initial EGFR or ALK targeted treatment) • Pembrolizumab monotherapy • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care For people with squamous NSCLC PD-L1 <50%: • Atezolizumab monotherapy		

	• Nivolumab monotherapy • Pembrolizumab monotherapy • Docetaxel • Best supportive care For people with squamous NSCLC PD-L1 >50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Best supportive care		
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Time-to-treatment discontinuation • Adverse effects of treatment • Health-related quality of life.	As per NICE final scope and in line with NICE reference case	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE final scope and in line with NICE reference case	N/A

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The use of pralsetinib in NSCLC is conditional on the presence of RET gene fusion. The economic modelling should include the costs associated with diagnostic testing for RET in people with advanced non-small-cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	If evidence allows, subgroup analysis by • Previous therapy	Separate treatment comparisons and cost-effectiveness analyses are conducted for untreated and pre-treated patients.	Due to the expected line agnostic indication, separate treatment comparisons and cost-effectiveness analyses are conducted for untreated and pre-treated patients. These correspond with the treatment naïve and prior systemic treatment subgroups in ARROW. Comparators were therefore separated into untreated and pre-treated treatments.
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations,	None	N/A

	guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 4. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 4: Description of the technology

UK approved name and brand name	UK approved name: pralsetinib Brand name: Gavreto™
Mechanism of action	Pralsetinib is a selective and highly potent TKI of WT *RET* and *RET*-altered kinases due to targeting fusions (KIF5B-RET and CCDC6-RET) and mutations (RET M918T and RET C634W), including gatekeeper mutations (namely RET V804M and RET V804L) associated with cabozantinib and vandetanib resistance. In NSCLC, the main oncogenic drivers are *RET* fusions. Certain *RET* fusion proteins and activating point mutations can have tumorigenic potential driving hyperactivation of downstream signalling pathways leading to uncontrolled cell proliferation. By selectively inhibiting *RET* kinase activity, pralsetinib inhibits the abnormal activation of such signalling pathways that lead to uncontrolled cell proliferation in multiple tumour types harbouring *RET* alterations (1, 4-6)
Marketing authorisation/CE mark status	An application for marketing authorisation has been submitted to the EMA for the following indication (1): [redacted] CHMP opinion is expected in [redacted], with marketing authorisation granted in [redacted]. A marketing authorisation application to the MHRA, via the EU reliance route has also been submitted. Marketing authorisation is anticipated to be granted in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for pralsetinib in the UK is as per the submitted indication for EMA and MHRA marketing authorisation.
Method of administration and dosage	Oral, 400 mg once-daily tablet. Dose may be adjusted based on tolerability. To be taken on an empty stomach (no food intake for at least two hours before and at least one hour after taking pralsetinib).

Additional tests or investigations	A confirmed diagnosis of *RET* fusion–positive NSCLC is required to prescribe pralsetinib. However, *RET* testing for people with NSCLC is included in the 2020/2021 National Genomic Test Directory (7), therefore, the identification of eligible patients for pralsetinib is not considered to result in added costs or an additional resource burden.
List price and average cost of a course of treatment	• List price of pralsetinib: £7,044 • Average cost of a course of treatment per untreated patient: [redacted] (as per undiscounted economic model results at list price) • Average cost of a course of treatment per pre-treated patient: [redacted] (as per undiscounted economic model results at list price)
Patient access scheme (if applicable)	Simple PAS: [redacted]

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

B.1.3.1 Disease overview

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (47,800) in 2017. It is responsible for 21% of all cancer deaths in the UK, making it the most common cause of cancer death. Approximately 34,600 people died of lung cancer in the UK in 2018 (8).

Lung cancer has two main subtypes, small cell lung cancer and non-small cell lung cancer (NSCLC), based upon the microscopic appearance of the tumour cells. These subtypes grow, spread and are treated in different ways, making their distinction important. NSCLC is the most common lung cancer, accounting for 85% of all cases (9).

Histologically, NSCLC is divided into three main types: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma is the most common type of NSCLC (40% of all lung cancers), arising from alveolar cells within the smaller airway epithelium (10). Squamous cell carcinomas arise from cells located in the airway epithelium and represent 25–30% of lung cancers. Finally, large cell carcinomas make up 5–10% of lung cancers and are characterised by undifferentiated neoplasms containing large cells with abundant amounts of cytoplasm and large nucleoli (10).

Clinical outcomes for NSCLC are related to the stage at time of diagnosis. Nearly 70% of patients with NSCLC present with inoperable locally advanced (stage IIIb) or metastatic

(stage IV) disease (9). The prognosis for patients with advanced disease is poor; 5-year survival rates for stage IIIb and stage IV NSCLC are 5% and <1%, respectively (11). Moreover, the COVID-19 pandemic has had profound effects on delays in diagnosis, treatment strategies and healthcare resource capacity (12), with one modelling study estimating that the pandemic will result in a 4.8–5.3% increase in the number of deaths due to lung cancer up to 5 years after diagnosis (13).

Genetic alterations and RET-fusion positive NSCLC

Over the course of the last two decades, the development of genetic testing has resulted in the identification of genetic alterations that play key roles as oncogenic drivers and predictors of responses to therapy in lung cancer. Oncogenic driver alterations cause constitutive activation of signalling pathways, leading to uncontrolled cell growth and proliferation. Approximately 75% of lung adenocarcinomas harbour drivers such as *KRAS*, EGFR, ALK, ROS1, *BRAF*, *MET*, *NTRK* and *RET*, among others (14).

RET is a proto-oncogene which encodes a single-pass transmembrane receptor tyrosine kinase required for normal embryonic development (5). In *RET* fusion–positive NSCLC, fusion events between sequences encoding the C-terminal *RET* kinase domain and gene partners such as KIF5B, CCDC6 or NCOA4 lead to the production of an oncogenic fusion protein with constitutively active tyrosine kinase activity (15, 16). As of April 2020, a total of 48 distinct RET fusion partners have been identified (17), with KIF5B being the most common fusion partner for *RET* rearrangements in patients with NSCLC (16, 18).

Each *RET* partner protein is thought to contain dimerisation domains such as the coiled-coil motif which mediates ligand-independent dimerisation, autophosphorylation and activation of *RET* (19), leading to the activation of downstream signalling cascades which promote tumour proliferation and tumour survival (20, 21).

RET fusions are seen in 1–2% of patients with NSCLC (20-22), most often in those with adenocarcinoma histology (18). Evidence suggests that *RET* is an independent oncogenic driver that is rarely found with other genetic alterations such as EGFR, *KRAS* or ALK (19). Moreover, *RET* rearrangements in patients with NSCLC are typically identified in younger (aged <60 years), female patients with minimal or no history of prior cigarette smoking (18, 23, 24). Reasons for early onset of lung cancer are unclear, but it is thought that familial susceptibility and Mendelian inheritance may be involved (25, 26). A poorer prognosis is observed in females with *RET* fusion–positive stage IV lung cancer compared with males,

where median PFS was comparatively shorter (4 months versus 6 months, respectively) (27).

Burden of disease

Common symptoms of NSCLC are mostly non-specific and may initially be disregarded by the patient, leading to the diagnosis of locally advanced or metastatic disease (28, 29). Common initial symptoms occurring in patients with NSCLC include cough, sputum with blood, chest pain, shortness of breath, weight loss, pain, fatigue, fever and dyspnoea. Patients with advanced (stage IV) disease experience more chest pain, shortness of breath, dyspnoea, weight loss and fatigue compared with patients with other stages of NSCLC (30). Research indicates that symptom severity can be a prognostic indicator of poorer clinical outcomes (31) and survival post-treatment (32). Additionally, pneumonia and pneumonitis are commonly seen in lung cancer patients, and the underlying disease is a confounding factor for these events (33, 34).

Metastases from NSCLC can cause more breathing difficulties, bone pain, abdominal or back pain, headache, weakness, seizures and speech difficulties (35). In particular, lung cancers are known to frequently metastasise to the central nervous system (CNS), with global registry datasets estimating the frequency of brain metastases at the time of diagnosis of stage IV disease at 25% (36). Based on multivariate analysis, risk factors for brain metastases include younger age, adenocarcinoma, tumour size >3 cm, tumour grade ≥II and node positive disease (37). The presence of CNS metastases in lung cancer is associated with a high disease burden, reduced life expectancy and poorer quality of life compared with other sites of metastases (38). The median survival of untreated NSCLC patients with CNS metastasis is poor at less than 2 months, while active treatment may only extend this to 4–6 months (39).

Patients with advanced NSCLC have worse health-related quality of life (HRQoL) compared to the general population and patients with other advanced cancers (40). In particular, depression is common in patients with lung cancer and is associated with severe symptoms and loss of functioning (41). In patients with newly diagnosed metastatic NSCLC, depression has been shown to predict worse survival (42, 43) and is associated with reduced QoL, disease progression, nausea and fatigue (42). Psychological distress is another common occurrence amongst patients affected by cancer. Patients with lung cancer report the highest rate of psychological distress compared with patients with other cancers; they are three times more likely to experience psychological distress (44). Psychological distress can also

be detrimental to treatment adherence and is associated with reduced HRQoL, poor health behaviours, higher mortality, and increased utilisation of healthcare services (44).

Lung cancer is also associated with a significant burden on caregivers, which can include social isolation, psychological impairment and poorer quality of life. A study investigating the consequences of caring for patients with lung cancer in five European countries (including the UK) concluded that caregivers had significantly higher odds of being diagnosed with depression, headache, insomnia and gastrointestinal symptoms, and worse HRQoL, compared with non-caregivers. Moreover, caregivers also shoulder an economic burden with higher annual indirect costs with presenteeism-related impairment (impairment while working) and overall work impairment (45). A modelling study estimated the mean cost of providing informal care to lung cancer patients at the end of life in England and Wales to be £73m, approximately one third of the total cost of care for this patient group (46).

B.1.3.2 Current treatment practice

Testing for genetic alterations

Over the past decade, cancer treatment has shifted away from the conventional approach of 'one size fits all' and increased focus on precision medicine based on genomic variant. Fundamental to this approach is the ability to characterise the molecular features of a tumour to not only determine tumour diagnosis and prognosis but to also guide treatment decisions and identify patients who may benefit from targeted therapies (47).

The importance of precision medicine to the future of healthcare at the NHS is acknowledged by the commitment from the Department of Health and Social Care to introduce widespread Next Generation Sequencing (NGS). Specifically, NHS England and NHS Improvement have committed to offer more extensive genomic testing to newly diagnosed cancer patients in 2021-22, so that by 2023 over 100,000 people a year will be able to access tests, including improved implementation of pan-cancer panels that are currently being rolled out (48).

In October 2018, the Genomic Medicine Service (GMS) was launched as part of the ambition of the NHS Long Term Plan, in which the NHS becomes the first healthcare service in the world to offer routine whole genome sequencing to specific groups of patients and deliver the first phase of a next-generation approach for the diagnosis and treatment of cancer (48). The GMS aims to provide comprehensive and equitable access to high quality genomic testing and management, regardless of condition and or geographical location,

thereby enabling faster diagnoses for rare diseases, ensuring patients receive the most effective treatments, and increasing cancer survival rates (49).

Genomic testing across the NHS GMS is standardised by a national genomic laboratory network made up of seven genomic laboratory hubs (GLHs), which are responsible for coordinating Next Generation Sequencing testing services for NHS patients in their geographical region (50). A key element of the GMS is the single National Genomic Test Directory that covers the use of all technologies from single genes to whole genome sequencing. This directory specifies the genomic tests that are commissioned by NHS England and stipulates which test and the technology by which it should be delivered for each clinical indication.

RET testing for people with NSCLC is included in the 2020/2021 National Genomic Test Directory, both as a multi-target NGS panel (test code M4.2) and as a *RET* rearrangement fluorescent in-situ hybridisation (FISH)/reverse transcription polymerase chain reaction (RT-PCR) (M4.7) (7). Therefore, screening for *RET* fusion-positive NSCLC is planned to be routinely carried out during genomic sequencing for oncogenic drivers in cancer. However, clinical expert advice obtained by Roche confirmed that testing for *RET* fusions is currently not routinely carried out, and there is considerable variation in the approaches taken to testing and turnaround times to obtaining results. Clinical experts also added that they hope to see improvements in the implementation of NGS testing for *RET* fusions by the end of 2021 (3).

Treatment for RET-fusion positive NSCLC

Currently, there is no NICE approved targeted treatment available for patients with *RET* fusion-positive NSCLC. Therefore, *RET* fusion-positive patients or patients with unconfirmed *RET* fusion status but display characteristics consistent with that population (i.e. non-squamous, younger, never smoked and ECOG PS 0–1) are currently managed with systemic treatment options for non squamous NSCLC (3). Given the low incidence of *RET* fusion-positive squamous patients, the focus of this appraisal is concentrated solely on non-squamous NSCLC patients, with the untreated population being the primary focus for the current appraisal.

Clinical experts confirmed to Roche in an advisory board meeting that patients without oncogenic drivers would receive immunotherapy with a pembrolizumab containing regimen, either as monotherapy for patients with PD-L1 expression ≥50% or in combination with platinum chemotherapy and pemetrexed for patients with PD-L1 expression <50%).

Pembrolizuamb + pemetrexed + platinum chemotherapy was assumed to be the treatment primarily used for this untreated patient population. It was noted during the advisory board meeting that very few patients currently receive the quadrupulet combination of atezolizumab, bevacizumab, carboplatin and paclitaxel due to the capacity constraints within chemotherapy units and the time required to administer this regimen (3).

In the second-line setting, clincial experts confirmed to Roche that a platinum chemotherapy containing regimen would be the preferred treatment for patients who had received pembrolizumab monotherapy, either as a platinum-doublet or carboplatin in combination with pemetrexed. Clinical expert advice also confirmed that patients would not be rechallenged with immunotherapy after receiving first-line pembrolizumab; patients who received pembrolizumab in combination with chemotherapy would therefore most likely receive docetaxel ± nintedanib. Beyond the second-line setting, patients may receive docetaxel ± nintedanib (if not previously received), best supportive care or be considered for clinical trials (3).

In accordance with the clinical expert advice received, the relevant comparators for the current appraisal are detailed below.

Table 5: Untreated and pre-treated comparators for the current appraisal

	Untreated	Pre-treated
Primary	Pembrolizumab + pemetrexed + platinum chemotherapy	Docetaxel monotherapy
Secondary	Pembrolizumab monotherapy	Docetaxel + nintedanib
Additional	--	Platinum-based chemotherapy +/- pemetrexed.

Limitations with current treatment options and the unmet need

Patients with *RET* fusion-positive NSCLC have not yet benefited from precision medicine and subsequently these patients have few treatments option and derive limited benefit from those available to them.

The need for targetted treatment options for *RET* fusion-positive NSCLC patients is greatest in the untreated setting. Immunotherapy containing regimens are frequently used in the first-line treatment of metastatic NSCLC. However, outcomes with immunotherapies in *RET* fusion-positive NSCLC are poor, as checkpoint inhibition has not shown benefit in this population, e.g. progression-free survival (PFS) ranged from 1.2 to 6.2 months among patients who receive pembrolizumab monotherapy (51, 52). Furthermore, objective response rate to immunotherapy was just 6% for NSCLC patients with *RET* rearrangements (53),

while real-world data from a Flatiron Health-Foundation Medicine Clinico-Genomic database of *RET* fusion-positive lung cancer demonstrated that median PFS and median overall survival (OS) in response to first-line immunotherapy was 4.2 months and 19.1 months, respectively (54). Moreover, treatment with immunotherapy may cause immune-related adverse events (AEs) which affect multiple organ systems, potentially resulting in complications such as pneumonitis, hepatitis and neurotoxic effects that can be fatal (55). Lacking targeted therapy, untreated patients with *RET* fusion-positive NSCLC are at risk of unnecessary potential toxicity associated with standard non-targeted therapies.

There is a paucity of outcome data for *RET* fusion-positive NSCLC patients in the second-line setting and beyond; however, historical outcomes seen with second-line chemotherapy regimens in patients without targetable molecular drivers are poor, with overall response rates ranging from 3.3% to 9.1%, median progression-free survival not exceeding 3.4 months and median OS ranging from 7.9 to 10.9 months (56, 57). Moreover, chemotherapeutic agents are also commonly associated with unpleasant AEs in patients with lung cancer, including diarrhoea, vomiting, constipation and anaemia (58, 59), which can have a detrimental effect on patient QoL (60). In addition, chemotherapy requires intravenous infusion and numerous hospital visits, which imposes a time burden on patients and facilities as well as having cost implications (61). Clinical experts confirmed to Roche that chemotherapy units in UK clinical practice are in crisis due to severe capacity constraints, therefore there is a desperate need for additional, non-chemotherapy based treatment regimens to alleviate the burden on these units (3).

Overall, there is accumulating evidence that the currently recommended treatment options for patients with advanced NSCLC and documented *RET* fusions do not offer the efficacy that has been achieved in patients with NSCLC and other identified oncogenes (such as EGFR and ALK). Therefore, *RET* fusion–positive NSCLC remains an unmet need that requires new therapeutic options to improve outcomes, generate cost savings and reduce the risk of unnecessary potential toxicity associated with standard non-targeted therapies, especially in the untreated setting.

B.1.3.3 Proposed position of pralsetinib in the treatment pathway

Pralsetinib is a highly selective and potent tyrosine kinase inhibitor of wild-type *RET* and *RET*-altered kinases due to targeting fusions (*KIF5B-RET* and *CCDC6-RET)* and mutations (*RET* M918T and *RET* C634W).

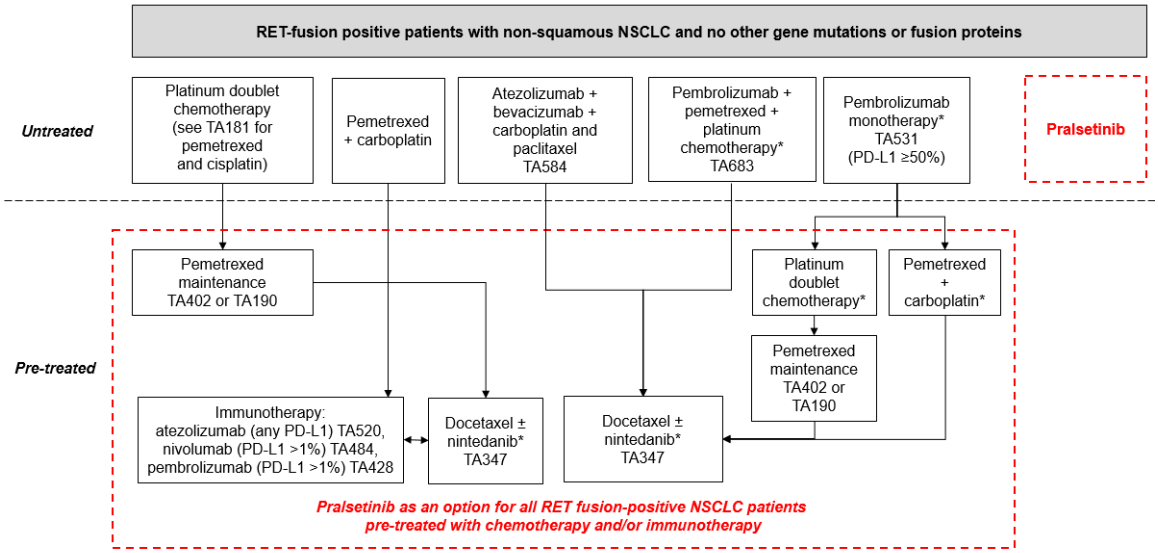
Certain *RET* fusion proteins and activating point mutations can have tumorigenic potential driving hyperactivation of downstream signalling pathways leading to uncontrolled cell proliferation. By selectively inhibiting *RET* kinase activity, pralsetinib inhibits the abnormal activation of such signalling pathways that lead to uncontrolled cell proliferation in multiple tumour types harbouring *RET* alterations (1, 4-6).

Pralsetinib offers new hope to adult patients with metastatic *RET* fusion–positive NSCLC, regardless of treatment history, exhibiting potent, durable and broad anti-tumour activity in both treatment-naïve patients as well as previously platinum-treated patients. Pralsetinib is generally well tolerated by patients, with a low discontinuation rate and manageable treatment-related AEs (62).

Pralsetinib has also demonstrated blood-brain-barrier penetration and anti-tumour activity against intracranial tumours in preclinical studies. Furthermore, pralsetinib has also shown strong intracranial activity in patients with *RET* fusion–positive NSCLC and measurable baseline brain metastases in the ongoing Phase 1/2 ARROW (BLU-667-1101) clinical study. Clinical outcomes also showed the inducement of intracranial complete responses (63).

A line agnostic marketing authorisation is anticipated for pralsetinib; however, based on the degree of unmet medical need and the potential benefits of earlier targeted treatment, the untreated population is the primary focus for pralsetinib in this appraisal. This position was validated by clinical experts in an advisory board and [redacted] who stated a preference for the usage of pralsetinib in the untreated population. In accordance with the anticipated indication, evidence for the pre-treated population is also provided in this submission and therefore pralsetinib is positioned as an additional treatment option for all adult patients with *RET* fusion–positive NSCLC, both in the untreated and pre-treated settings.

Figure 2: Proposed positioning of pralsetinib in treatment pathway for *RET* fusion-positive non-squamous NSCLC



Dotted red line indicates proposed positioning of pralsetinib
NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1
*indicates relevant comparator for the current appraisal. Note, following advice with clinical experts at an advisory board, it was decided pemetrexed + carboplatin could be encompassed within platinum doublet chemotherapy due to similarities between the treatment regimens

B.1.4 Equality considerations

No equality issues have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 6: Clinical effectiveness evidence

Study	BLU-667-1101, ARROW, NCT03037385 (64)				
Study design	Phase I/II, multicentre, non-randomised, open-label, multi-cohort study				
Population	Patients with advanced, unresectable, *RET* fusion-positive NSCLC and other *RET* altered solid tumours				
Intervention(s)	Pralsetinib				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓
	No			**No**	
Rationale for use/non-use in the model	ARROW is a Phase I/II trial providing efficacy and safety evidence for pralsetinib in patients with *RET* fusion-positive NSCLC. Data from ARROW (clinical cut-off date 06 November 2020) were used to inform the efficacy and safety of pralsetinib in the economic model.				
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Response rate Time-to-treatment discontinuation Adverse events Health-related quality of life				
All other reported outcomes	Duration of response Clinical benefit rate Disease control rate CNS activity				

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

Unless otherwise stated, information on the ARROW study was sourced from the primary clinical study report (65).

B.2.3.1 Study design

ARROW is a Phase 1/2, open-label, first-in-human (FIH) study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and antineoplastic activity of pralsetinib in patients with advanced, unresectable, *RET*-altered NSCLC, medullary thyroid carcinoma (MTC), and other *RET*-altered solid tumours. The study included a Phase 1 dose escalation part to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pralsetinib, followed by a Phase 2 expansion part to assess the clinical efficacy of pralsetinib in specific tumour types and treatment settings (measured primarily by objective response rate [ORR]) and further define the safety and tolerability at the recommended Phase 2 dose (RP2D). Phase 1 ran until the RP2D was determined, at which point Phase 2 was initiated.

The minimum duration of patient participation was approximately 3 months, including a screening period to assess study eligibility up to 4 weeks (28 days); a treatment period of at least 1 cycle (28 days); an end-of-treatment (EOT) visit at least 14 ± 7 days following the last dose of study drug; and a follow-up telephone contact for resolution of any AEs 30 days (+ 7 days) after the last dose of pralsetinib, or at the time the patient initiates another antineoplastic therapy. After cycle one, patients could continue to receive pralsetinib until precluded by toxicity, noncompliance, withdrawal of consent, death, or closure of the study. Patients with progressive disease could remain on treatment if in the opinion of the Investigator the patient has benefited from the pralsetinib therapy, and it was clearly in the best medical interest of the patient to remain on treatment. A patient was considered to have completed the study if he/she had completed all required visits.

Phase 1

A Bayesian optimal interval (BOIN) design was employed for Phase 1. The MTD was determined based on isotonic regression and was the dose for which the isotonic estimate of the toxicity rate is closest to a target toxicity rate of 30%. Alternatives under which decision errors were minimised were: 18% (subtherapeutic) and 42% (overly toxic).

To limit the number of patients treated at a subtherapeutic dose, patient cohorts consisted of 1–3 patients for the first three pralsetinib dose levels at a once-daily schedule (i.e., 30, 60, and 100 mg) and of 3–6 patients for the rest of the dose levels (i.e., 200, 300, 400, and 600 mg), as well as for the twice-daily schedule (i.e., 100/100 mg and 200/100 mg).

Enrolment could continue until up to 12 patients were treated and evaluable for dose-limiting toxicity (DLT) at a given dose level. The total number of patients to be enrolled during the

dose escalation part of the study could vary depending on the toxicity profile of pralsetinib and the number of dose levels tested prior to reaching the MTD.

Patients treated at doses >120 mg per day were required to have MTC or a *RET*-altered solid tumour per local assessment of tumour tissue and/or blood. Additionally, these patients could be enrolled into an enrichment cohort, if it previously included <12 patients evaluable for dose-limiting toxicity (DLT), was reviewed at a dose escalation meeting, and did not exceed the MTD.

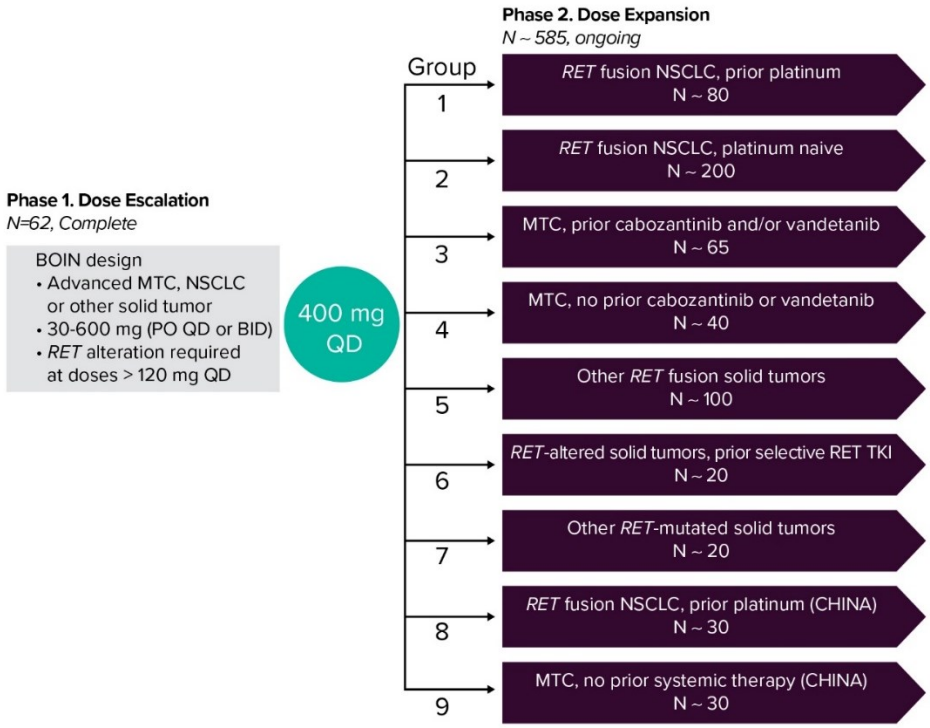
Phase 2

Phase 2 was performed to provide a more complete assessment of safety, PK, pharmacodynamics, and anti-tumour activity in patients with different types of *RET*-driven malignancies treated with pralsetinib at the RP2D, as determined in Phase 1. Patients were enrolled into 1 of 7 groups based on their disease type and prior therapy status (if applicable). With the exception of Groups 3 and 4, patients had to have an oncogenic *RET* fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumour, as determined by local testing of tumour or circulating tumour nucleic acid in blood.

- Group 1: NSCLC with a *RET* fusion previously treated with a platinum-based chemotherapy (n ~80);
- Group 2: NSCLC with a *RET* fusion not previously treated with a platinum-based chemotherapy, including those who had not had any systemic therapy (n ~200);
- Group 3: MTC previously treated with cabozantinib and/or vandetanib (n ~65);
- Group 4: MTC not previously treated with cabozantinib or vandetanib (n ~40);
- Group 5: Other solid tumours with a *RET* fusion previously treated with standard of care appropriate for the tumour type (n ~100);
- Group 6:Any solid tumours with a *RET* alteration (fusion or mutation) previously treated with a selective *RET* tyrosine kinase inhibitor (TKI) (n ~20);
- Group 7: Other solid tumours with a *RET* mutation previously treated with standard of care appropriate for the tumour type (n ~20)

Note, ongoing Groups 8 and 9 (NSCLC and MTC patients from China only) also contribute data in the safety analysis but not in the efficacy analysis

Figure 3: ARROW design schema (Phase 1 and Phase 2)



Eligible patients received pralsetinib until progression of disease, intolerance, or any of the other reasons for discontinuation of treatment. Study treatment was administered in 28-day "cycles", with clinic visits for safety and PK on D1 of each cycle. Throughout treatment, safety was assessed via AE evaluation, physical exam, and vital signs, clinical laboratory assessments, and electrocardiogram (ECG). In Phase 2, patients periodically completed QoL assessments (EORTC QLQ-C30).

Following discontinuation of study treatment, patients were to be seen for an EOT visit at least 14 ± 7 days following the last dose of pralsetinib, and to have a follow-up telephone contact for resolution of any AEs 30 days (+ 7 days) after the last dose of pralsetinib or at the time the patient initiates another antineoplastic therapy. Patients without documented progressive disease (PD) at the time of treatment discontinuation were to be followed for PFS until withdrawal of consent, death, or loss to follow-up, with tumour assessments every 3 months until documented PD or initiation of another antineoplastic therapy. Patients were additionally asked to participate in post-treatment OS follow-up, including telephone contacts every 3 months until death or study closure. The end of the study was defined as the time that the last patient completes his/her last visit, including assessments performed as part of the PFS and OS follow-up.

B.2.3.2 Summary of study methodology

	ARROW (NCT03037385)
Settings and locations of data collection	Phase 1 was completed with 62 patients (58 from the USA, 4 from Europe). Phase 2 dose expansion is ongoing in 79 centres and 13 countries: Belgium, China France, Germany, Hong Kong, Italy, South Korea, the Netherlands, Singapore, Spain, Taiwan, the UK and the USA
Trial design	Phase 1/2, multicentre, non-randomised, open-label, multi-cohort study in patients with *RET* fusion–positive NSCLC and other advanced solid tumours

Eligibility criteria	**Key inclusion criteria**
	• ≥18 years of age
	• Phase 1 diagnosis: pathologically documented, definitively diagnosed non-resectable advanced solid tumour
	  ○ All patients treated at doses >120 mg per day must have MTC, or a *RET*-altered solid tumour per local assessment of tumour tissue and/or blood.
	  ○ Phase 1 enrichment patients must have MTC or a *RET*-altered solid tumour per local assessment of tumour tissue and/or blood.
	• Phase 2 diagnosis: all patients (exc. patients with MTC enrolled in Groups 3, 4, and 9) must have an oncogenic *RET* fusion or mutation (exc. synonymous, frameshift, and nonsense mutations) solid tumour, as determined by local testing of tumour or circulating tumour nucleic acid in blood; as detailed below
	  ○ Group 1 –pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a *RET* fusion previously treated with a platinum-based chemotherapy
	  ○ Group 2 –pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a *RET* fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug.
	  ○ Group 3 – pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was previously treated with cabozantinib and/or vandetanib.
	  ○ Group 4 – pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was not previously treated with cabozantinib or vandetanib.
	  ○ Group 5 - pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic *RET* fusion, have previously received SOC appropriate for their tumour type (unless there is no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate), and must not eligible for any of the other groups.

	○ Group 6 - pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic *RET* fusion or mutation, previously treated with a selective TKI that inhibits *RET*, such as selpercatinib. ○ Group 7 - pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic *RET* mutation previously treated with SOC appropriate for the tumour type and not eligible for any of the other groups. ○ Group 8 - pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a *RET* fusion that was previously treated with a platinum-based chemotherapy (China only) ○ Group 9 - pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit, and was not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced or metastatic disease (China only). • Patients must have non-resectable disease. • Dose expansion (Phase 2) patients in all groups (except Group 7) must have measurable disease per RECIST v1.1 (or RANO if appropriate). • Consent to provide tumour tissue (archived, if available or a fresh biopsy) for *RET* status confirmation and willing to consider an on-treatment tumour biopsy, if considered safe and medically feasible by the treating Investigator. For Phase 2, Group 6, patients are required to undergo a pre-treatment biopsy to define baseline *RET* status in tumour tissue. • ECOG PS of 0–1. **<u>Key exclusion criteria (see protocol for further details)</u>** • Patient's cancer has a known primary driver alteration other than *RET*. For example, NSCLC with a targetable mutation in EGFR, ALK, ROS1, or BRAF • Patient has any of the following within 14 days prior to the first dose of study drug ○ Platelet count < 75 × 10^9/L ○ Absolute neutrophil count (ANC) < 1.0 × 10^9/L ○ Haemoglobin < 9.0 g/dL (red blood cell transfusion and erythropoietin may be used to reach at least 9.0 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug) ○ Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present. ○ Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease. ○ Estimated (Cockroft-Gault formula) or measured creatinine clearance < 40 mL/min. ○ Total serum phosphorous > 5.5 mg/dL

	• QTcF > 470 msec. Patient has a history of prolonged QT syndrome or Torsades de pointes. Patient has a familial history of prolonged QT syndrome. • Clinically significant, uncontrolled, cardiovascular disease including congestive heart failure Grade III or IV according to the New York Heart Association • Central nervous system (CNS) metastases or a primary CNS tumour that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease • Clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis • Any systemic anticancer therapy (except for immunotherapy or other antibody therapies) and all forms of radiotherapy, within 14 days or 5 half-lives prior to the first dose of study drug. Pralsetinib may be started within these washout periods if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval • Any immunotherapy or other antibody therapy within 28 days prior to the first dose of study drug (immune related toxicities must have resolved to < Grade 2 prior to starting pralsetinib). • Previous *RET* inhibitor treatment in Phase 2 Groups 1–5 and 7 • Received neutrophil growth factor support within 14 days of the first dose of study drug. • Major surgical procedure within 14 days of the first dose of study drug • Treatment with a prohibited medication or herbal remedy (as specified that cannot be discontinued at least 2 weeks before the start of study drug administration • History of another primary malignancy that has been diagnosed or required therapy (except maintenance anti-hormonal therapy) within the past year
Trial drugs and concomitant medications	**Trial drugs** ***Phase 1 (dose escalation)*** • Pralsetinib was administered QD to patients enrolled at the first 3 dose levels (i.e., 30, 60, and 100 mg) • After the dose level of 200 mg, BID schedules were also explored, i.e., 100/100 mg *100 mg in the morning and 100 mg in the evening) and the 200/100 mg (i.e., 200 mg in the morning and 100 mg in the evening). • BID schedules were abandoned and further QD dose levels were explored: 200, 300, 400, and 600 mg ***Phase 2*** • All patients received pralsetinib orally in a QD schedule at a dose of 400 mg. **Dose modifications** ***Phase 1*** • To minimise the number of patients treated at potentially inactive doses, intra-patient dose escalation was permitted after a patient had

	completed ≥ 2 cycles of treatment (1 cycle was 28 days) without experiencing Grade 3/4 AE related to study drug or a DLT • A temporary discontinuation (up to 2 weeks) in pralsetinib dosing was allowed for patients who required an interruption (e.g., for surgery or another procedure) during the treatment period. Pralsetinib was to be discontinued 48 hours before the procedure and resumed 48 hours after the procedure had been completed. • Patients who experienced a DLT interrupted administration of pralsetinib and were followed until the DLT resolved to Grade ≤ 1 or until the patient's baseline value was achieved, if higher. After resolution of the AE, with a maximum of 2 weeks' dose interruption, the patient could resume therapy with a reduction of 1 dose level. A maximum of 3 dose reductions were permitted for any patient ***Phase 2*** • Pralsetinib dose reductions to below 100 mg QD were not permitted. If a patient required dose reduction below these dose levels, study treatment was to be discontinued. • Specific dose modification recommendations were made for pralsetinib-related AEs, specifically for the ADRs of pneumonitis, pneumonia/lung infections, tumour lysis syndrome, hyperphosphatemia, and hypertension • Re-escalation after dose modification for AEs was discouraged. However, if in the opinion of the treating Investigator re-escalation was warranted, this was to be undertaken after consultation with the Sponsor. In no circumstances was a patient to receive a dose > 400 mg QD **<u>Concomitant medications</u>** **Prohibited concomitant medications:** • Strong inhibitors as well as inducers of CYP3A4. If co-administration of pralsetinib with a strong CYP3A inhibitor cannot be avoided, the dose of pralsetinib should be reduced. • Any investigational agent or device other than pralsetinib, including commercially available agents that are investigational for the treatment of the patient's underlying malignancy. • Any antineoplastic treatment other than study drug. • Neutrophil growth factor support is prohibited within 14 days before C1D1 and throughout C1, unless the patient experiences a DLT of neutropenia. • Medications that are sensitive CYP2C8, CYP3A4, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K substrates with known drug-drug interaction potential should be used with caution **Permitted concomitant medications:** • Medications and treatments other than those specified above including palliative and supportive care for disease-related symptoms, were permitted during the study
Primary outcome	**Phase 2 primary endpoint:**

	• Objective response rate by RECIST v1.1 criteria by patients' disease type, and/or *RET*-altered status if applicable, and/or prior treatment status if appropriate • Safety and tolerability
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • Duration of response, clinical benefit rate, disease control rate, progression-free survival, overall survival, in all patients by disease type and/or *RET*-altered status, if applicable, and/or prior treatment status, if appropriate **Exploratory objectives:** • Time-to-off treatment • **CNS activity assessed by BICR** • Changes in patient-reported outcomes as assessed by the EORTC QLQ-C30 questionnaire instruments
Pre-planned subgroups	**Pre-planned subgroup analyses** • ORR by *RET* genotype and prior anticancer therapy.

ADR, adverse drug reaction; AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BID, twice-daily; BICR, blinded independent central review; C1D1, cycle 1 day 1; CNS, central nervous system; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of life questionnaire; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily; QTcF, QT-interval of the 12-lead electrocardiogram corrected for heart rate by Fridericia's formula; RANO, response assessment in neuro-oncology; RECIST, Response Evaluation Criteria in Solid Tumours; *RET*, rearranged during transfection; SOC, standard of care; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal

B.2.3.3 Patient demographics and baseline characteristics

The ARROW study enrolled adult patients with a pathologically documented, diagnosed, unresectable advanced solid tumour. At the data cut-off of 06 November 2020, a total of 528 patients with any indication (NSCLC, MTC and other *RET*-altered solid tumours) received ≥1 dose of pralsetinib 400 mg once daily (QD). Patient numbers for the measurable disease population (MDP) and efficacy population are presented below.

Table 7: *RET* fusion–positive patients with NSCLC treated at 400 mg QD

	Measurable Disease Population[a] n=216	Efficacy Population[b] n=233
Prior systemic treatment, n (%)	148 (68.5)	158 (67.8)
Prior platinum treatment	126 (58.3)	136 (58.4)
No prior platinum treatment	22 (10.2)	22 (9.4)
No prior systemic treatment, n (%)	68 (31.5)	75 (32.2)

NSCLC, non-small cell lung cancer; QD, once daily; *RET*, rearranged during transfection.
[a]All patients in the efficacy population who had measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for tumour type) at baseline according to blinded central review and sufficient evidence of a RET alteration.
[b]All patients with RET fusion–positive NSCLC in the safety population who were initiated with 400 mg pralsetinib on or prior to 22 May 2020. The efficacy population was the primary population for efficacy analysis. Patients with prior selective RET inhibitor treatment were explored separately and were not included in any defined efficacy subgroups.
Data cut-off date 06 Nov 2020; enrolment cut-off date 22 May 2020.

The demographic and baseline characteristics of patients with *RET* fusion–positive NSCLC treated at 400 mg QD both in the MDP and the efficacy population are summarised in Table 8.

Among all 216 patients in the NSCLC MDP, 51.9% were female, and 66.5% were <65 years of age. Most patients in the MDP were White (52.3%) or Asian (38.4%) and 38.0% had a history of/current CNS metastasis. A median of 1.0 (range 0, 6) prior lines of therapy were received. Prior therapies included platinum-based chemotherapy (58.3%), PD-(L)1/ inhibitors (30.6%) and multikinase inhibitors (MKIs) (18.5%). Eighty-two patients (38.0%) had previously received radiation.

Similarly, to the MDP demographic and baseline characteristics, of the 233 patients in the efficacy population, 52.4% were female and 37.3% had history of/current CNS metastases. Most patients in the efficacy population were White (51.9%) or Asian (39.5%) and were <65 years of age (62.2%). The median (range) age of this patient population was 60.0 (26–87) years of age.

Table 8: Summary of demographic and baseline characteristics of patients with *RET* fusion–positive NSCLC treated at 400 mg QD in the MDP and efficacy population

	Measurable Disease Population			Efficacy Population		
	All *RET* positive NSCLC n=216	Prior Systemic Treatment n=148	Treatment naïve n=68	All *RET* positive NSCLC n=233	Prior Systemic Treatment n=158	Treatment naïve n=75

Demographics						
Median age, years (range)	60.0 (26, 87)	60.0 (26, 85)	60.5 (30, 87)	60.0 (26, 87)	59.5 (26, 85)	63.0 (30, 87)
≥65, %	37.5	35.1	42.6	37.8	34.2	45.3
Sex, female, %	51.9	53.4	48.5	52.4	54.4	48.0
Race, %						
White	52.3	43.9	70.6	51.9	43.7	69.3
Asian	38.4	46.6	20.6	39.5	47.5	22.7
Native Hawaiian/ Pacific Islander	0.9	0.7	1.5	0.9	0.6	1.3
Other	0.9	1.4	0.0	0.9	1.3	0.0
Unknown	7.4	7.4	7.4	6.9	7.0	6.7
Baseline characteristics						
ECOG performance status, %[a]						
0	33.8	29.7	42.6	33.5	29.7	41.3
1	63.4	66.9	55.9	63.9	67.1	57.3
2	2.8	3.4	1.5	2.6	3.2	1.3
Histology type, %						
Adenocarcinoma	95.8	94.6	98.5	96.1	94.9	98.7
Squamous	1.4	1.4	1.5	1.3	1.3	1.3
Undifferentiated	<1.0	<1.0	0.0	<1.0	<1.0	0.0
Other	2.3	3.4	0.0	2.1	3.2	0.0
Brain metastases %	38.0	40.5	32.4	37.3	39.2	33.3
Smoking history, %						
Never	61.6	65.5	52.9	62.2	65.8	54.7
Former	34.3	31.8	39.7	33.5	31.6	37.3
Current	2.8	1.4	5.9	2.6	1.3	5.3
Unknown	1.4	1.4	1.5	1.7	1.3	2.7
***RET* fusion partner, %**						
KIF5B	71.3	73.0	67.6	70.4	72.2	66.7
CCDC6	18.1	17.6	19.1	17.6	17.7	17.3
NCOA4	0.0	0.0	0.0	<1.0	0.0	1.3
Other	10.6	9.5	13.2	11.6	10.1	14.7
Prior treatment, %						
Chemotherapy	59.2	86.5	0.0	59.2	87.3	0.0
Platinum chemotherapy	58.3	85.1	0.0	58.4	86.1	0.0
PD-(L)1 inhibitors	30.6	44.6	0.0	29.6	43.7	0.0

Multikinase inhibitor(s)	18.5	27.0	0.0	18.9	27.8	0.0
Prior Radiation therapy	38.0	46.6	19.1	38.6	46.8	21.3
Prior cancer related surgeries/ procedures	47.2	50.7	39.7	49.8	51.9	45.3

ECOG, Eastern Cooperative Oncology Group; PD-(L) 1, programmed death-(ligand) 1; *RET*, rearranged during transfection

The ARROW patient disposition in the *RET* fusion–positive NSCLC MDP and efficacy population is presented in Appendix D.

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

B.2.4.1 Sample size justification

As pralsetinib has potent activity against *RET* fusions, activating mutations and resistance mutations, the hypothesis and sample size calculation based on ORR as per RECIST v1.1 is specific to the response-evaluable *RET*-altered patients (excluding groups 4, 6, and 7) for each Phase 2 expansion group.

- Group 1: The sample size of approximately 80 *RET*-fusion NSCLC patients who previously received treatment with a platinum-based chemotherapy will provide > 95% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.23 versus the alternative ORR=0.5.
- Group 2: The sample size of approximately 170 treatment naïve (1st line) *RET* fusion NSCLC patients will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.48 versus the alternative ORR=0.61
- Group 3: The sample size of approximately 65 MTC patients previously treated with cabozantinib and/or vandetanib will provide > 90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.2 versus the alternative ORR=0.4.
- Group 4: The sample size of approximately 40 MTC patients not previously treated with cabozantinib or vandetanib will be enrolled for exploratory analysis
- Group 5: The sample size of approximately 40 patients who have solid tumours with a *RET* fusion previously treated with SOC appropriate for the disease type will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.1 versus the alternative ORR=0.3.

- Group 6: The sample size of approximately 20 patients with solid tumours with a *RET* alternation (fusion or mutation) previously treated with a selective *RET* inhibitor will be enrolled for exploratory analysis.
- Group 7: The sample size of approximately 20 patients who have solid tumours with an activating *RET* mutation previously treated with SOC will be enrolled for exploratory analysis.

B.2.4.2 Analysis populations

Different populations were considered for the efficacy analysis of Phase 2:

- Efficacy population
- *RET*-altered measurable disease population
- Response-evaluable population

Note, the efficacy population was limited to patients who enrolled on or prior to 22 May 2020 to ensure enough follow-up time to measure ORR and other endpoints. However, considering that OS and PFS are time-to-event endpoints that can be considered for any follow-up time, it was deemed appropriate to consider patients enrolled at any time for these endpoints. A population referred to as the unrestricted efficacy population is presented to demonstrate efficacy analyses of OS and PFS. The unrestricted efficacy population is a broader population of patients with *RET* fusion–positive NSCLC and is not defined in the ARROW clinical study protocol.

Table 9: Definitions of ARROW analysis populations

Population	Definition
Safety population	All patients who were initiated with 400 mg QD pralsetinib.
Efficacy population	All patients with *RET* fusion–positive NSCLC in the safety population who were initiated with 400 mg pralsetinib on or prior to 22 May 2020. The efficacy population was the primary population for efficacy analysis. Patients with prior selective *RET* inhibitor treatment were explored separately and were not included in any defined efficacy subgroups.
Measurable disease population	All patients in the efficacy population who had measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for tumour type) at baseline according to blinded central review and sufficient evidence of a *RET* alteration. The *RET*-altered measurable disease population provides an assessment of the activity of pralsetinib in a mechanistically relevant population.
Unrestricted efficacy population	All patients in the safety population with *RET* fusion–positive NSCLC who were initiated with 400 mg pralsetinib regardless of date of initial dosing. This population is broader than the efficacy population and is considered adequate to assess time-to-event for PFS and OS.
Response-evaluable population	Patients in the efficacy population who had measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for disease type) at baseline, and had at least one evaluable post-baseline disease response assessment performed and had no major protocol violation. *Note: the RE population was used for the efficacy analyses of CNS activity only*

CNS, central nervous system; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RANO, response assessment in neuro-oncology; RE, response evaluable; RECIST, response evaluation criteria in solid tumours; *RET*, rearranged during transfection

B.2.4.3 Efficacy analysis

B.2.4.3.1 Primary efficacy endpoint

The primary efficacy endpoint of ARROW Phase 2 trial was ORR. ORR analyses were summarised based on the measurable disease population and the efficacy population. Note: Phase 1 patients who received pralsetinib at a starting dose of 400 mg QD were pooled together with patients in Phase 2 for the efficacy analyses.

Table 10: Primary efficacy endpoint of ARROW Phase 2

Outcome	Definition	Analysis Methodology	Analysis Populations included
ORR	Proportion of patients with a confirmed response: CR or PR (for at least two assessments with at least 28 days apart and no PD in between)	Two-sided 95% CI based on the exact binomial distribution (Clopper-Pearson). The tumour response and progression were assessed by RECIST v1.1 criterion (or RANO criteria).	Measurable disease population, Efficacy population

CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumours.

ORR was defined as the proportion of patients with confirmed best overall response (BOR) of complete response (CR) or partial response (PR) for ≥2 assessments with ≥28 days and no PD in between. Each patient's BOR was derived based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The response-evaluable population was used for the primary efficacy endpoint as a sensitivity analysis for BOR. BOR was summarised by count and frequency for the CR, PR, stable disease (SD), PD or not evaluable (NE) categories. ORR was also analysed by *RET* genotype (KIF5B, CCDC6 and others), and further analysed by age group, grouped race, geographic region and sex

B.2.4.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints of the ARROW Phase 2 trial included DOR, CBR, DCR, PFS, and OS outcomes.

Table 11: Secondary efficacy endpoints of ARROW Phase 2

Outcome	Definition	Analysis Methodology	Analysis Population included
DOR	The time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurred first.	KM methods and included the estimated median with two-sided 95% CI and 25th and 75th percentiles. DOR at specific time-points was computed, along with standard errors using Greenwood's formula	Measurable disease population, Efficacy population
CBR	The rate of CR, PR, or stable disease lasting at least 16 weeks (i.e., four 28-day cycles) from the first dose date	CBR was analysed and summarised using the same methods as ORR	Measurable disease population, Efficacy population

DCR	The proportion of patients with a confirmed CR/PR, or SD, per RECIST v1.1 (or RANO if appropriate)	DCR was analysed and summarised using the same methods as ORR	Measurable disease population, Efficacy population
PFS	The time from the first dose of pralsetinib to the date of first documented PD or death due to any cause, whichever occurred first. Patients without PD or death at time of data cut-off will be censored at their last valid assessment	KM methods, the estimated median with two-sided 95% CI and 25th and 75th percentiles were used. The CI calculation was based on identity (i.e., linear) transformation. PFS at specific time-points computed, along with the standard errors, using Greenwood's formula PFS will be displayed with KM plots	Unrestricted efficacy population, Efficacy population
OS	The time from the first dose of pralsetinib to the date of death due to any causes. Patients who are still alive or lost to follow-up will be censored at the last known alive date	OS was analysed and summarised in a same manner as for PFS	Unrestricted efficacy population, Efficacy population

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; KM, Kaplan–Meier; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

Time-to-event data (DOR, PFS, OS and TTOT) were summarised and analysed using the Kaplan–Meier (KM) method, including the estimated median with 95% CIs. The estimated median with two-sided 95% CI and 25th and 75th percentiles was provided. The confidence interval calculation was based on identity (i.e., linear) transformation. Outcomes were recorded at specific time-points (e.g. 3-, 6-, 9- and 12- months, and every 6 months after the 12-month time-point) and computed, alongside standard errors, using Greenwood's formula. Endpoints involving response assessment were primarily based on BICR data. The investigator assessment data were analysed using the same analysis method as supportive analyses.

B.2.4.3.3 Patient reported outcomes

PROs are only available for the primary analysis (CCOD 18 November 2019).

Patients completed the EORTC QLQ-C30 on D1 of Cycles 1 through 12, a 30-item questionnaire used to evaluate QoL. If the patient did not complete the questionnaire at C1D1 (i.e., for a baseline), then it was not completed at subsequent cycles. This

questionnaire included five functional domains (physical, cognitive, role, emotional, and social) and a global health status scale of 0 to 100.

B.2.4.3.4 Safety reporting and analysis

All safety analyses were performed on the safety population. All safety data were summarised by grouped dose level based on the safety population, unless otherwise specified. Safety was evaluated by the incidence of causality, intensity, seriousness, and type of AEs, and by the patient's vital signs, physical examination, Eastern Cooperative Oncology Group performance status scores, clinical laboratory test results, and ECG data.

Table 12: Safety analysis for ARROW Phase 1 and Phase 2

Safety Data	Methods of Analysis
AEs	AEs and SAEs were recorded on the CRF from screening visit through 30 days after the last dose of study drug. SAEs that were assessed as possibly or probably related to study treatment that occur >30 days post-treatment were reported.
AESI	AESI categories were defined by groups of selected and relevant preferred terms. Three identified AESI categories were pneumonia, pneumonitis and tumour lysis syndrome. Adjacent events Time to onset Time to improvement Time to resolution/return to baseline
Grouped AEs	Neutropenia and neutrophil count decrease were combined into grouped neutropenia AEs. Analysis was presented for grouped neutropenia.
SAEs and Deaths	All SAEs were reported; whether they were considered causally related to pralsetinib or not. SAEs assessed as possibly or probably related to pralsetinib were reported even if the occurrence was >30 days after the last dose of the study drug. Death was recorded during the active treatment phase and within 30 days after the last date of the study treatment.

AE, adverse event; AESI, adverse events of special interest; CRF, case report form; SAE, serious adverse event.

B.2.4.4 Relevant analysis methods

B.2.4.4.1 Time-to-off treatment

Time-to-off treatment (TTOT) is defined as the time from the start of therapy to the treatment discontinuation for any reason. TTOT analyses were performed in the unrestricted efficacy population to support the economic model of pralsetinib for patients with *RET* fusion–positive NSCLC.

B.2.4.4.2 Central nervous system activity

Definition of CNS metastases activity:

- CNS metastases lesion response (CR) was defined as disappearance of all target CNS/brain lesions.
- CNS metastases lesion response (PR) was defined as at least 30% decrease in the sum of diameters of any CNS/brain lesion.
- CNS metastases progression was defined as either at least 20% increase in the sum of diameters of target CNS/brain lesions or unequivocal progression of any CNS/brain lesions or the identification of new CNS/brain lesions.
- CNS metastases SD was defined as neither sufficient shrinkage to qualify for PR no sufficient increase to qualify for PD for target/non-target CNS/brain lesions.

NSCLC patients' brain tumour lesions were assessed by RECIST v1.1. CNS metastases activity analysis followed the same methods used for the primary efficacy endpoint, ORR.

CNS activity or a primary CNS tumour (that were associated with progressive neurological symptoms or required increasing doses of corticosteroids to control the CNS disease) were evaluated in the response-evaluable population.

Disposition for the CNS analysis population included *RET* fusion–positive NSCLC patients who had measurable lesions in the CNS or brain, including brainstem and cerebellum at baseline according to RECIST v1.1 by BICR data and did not have radiotherapy or radiosurgery to brain within 2 months before dosed with 400 mg QD of pralsetinib.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

No randomised clinical trials for pralsetinib were identified in the systematic literature review, therefore a quality assessment of the clinical effectiveness evidence was not conducted.

B.2.6 Clinical effectiveness results of the relevant trials

The analysis presented in this submission refer to the most recent data cut-off of 06 November 2020 (66, 67), except for PROs where data were only available for data cut-off of 18 November 2019 (65). Data for the primary and secondary response endpoints were assessed in the Measurable Disease Population. Time-to-event endpoints were measured in the unrestricted efficacy population, which includes patients who were initiated with 400 mg pralsetinib regardless of date of initial dosing.

B.2.6.1 Primary efficacy endpoint

Overall response rate

Measurable disease population

ORR in patients with *RET* fusion–positive NSCLC treated at 400 mg QD in the overall MDP (n=216) was 68.5% (95%CI: 61.9, 74.7). ORR results were similar among patients in this population irrespective of prior treatment (67).

- *Treatment-naïve subgroup* (n=68): ORR was 79.4% (95% CI: 67.9, 88.3)
- *Prior systemic treatment subgroup* (n=148): ORR was 63.5% (95% CI: 55.2, 71.3)

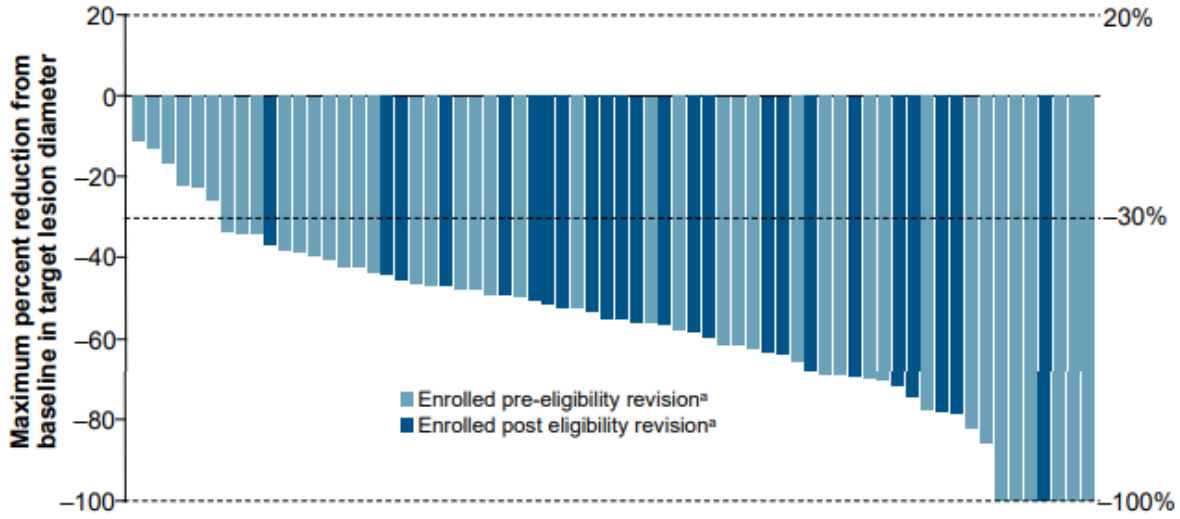
Table 13: ORR in patients with *RET* fusion–positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC N=216	All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
ORR, % (95% CI)	69 (62, 75)	79 (68, 88)	74 (59, 87)	88 (69, 98)	64 (55, 71)	62 (53, 70)	73 (50, 89)
Best Overall Response, n (%)							
CR	9 (4)	4 (6)	4 (9)	0	5 (3)	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	89 (60)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	41 (28)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	7 (5)	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (4)	6 (5)	0

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.
CR, complete response; NE, not estimated; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease
CCOD: 06 November 2020

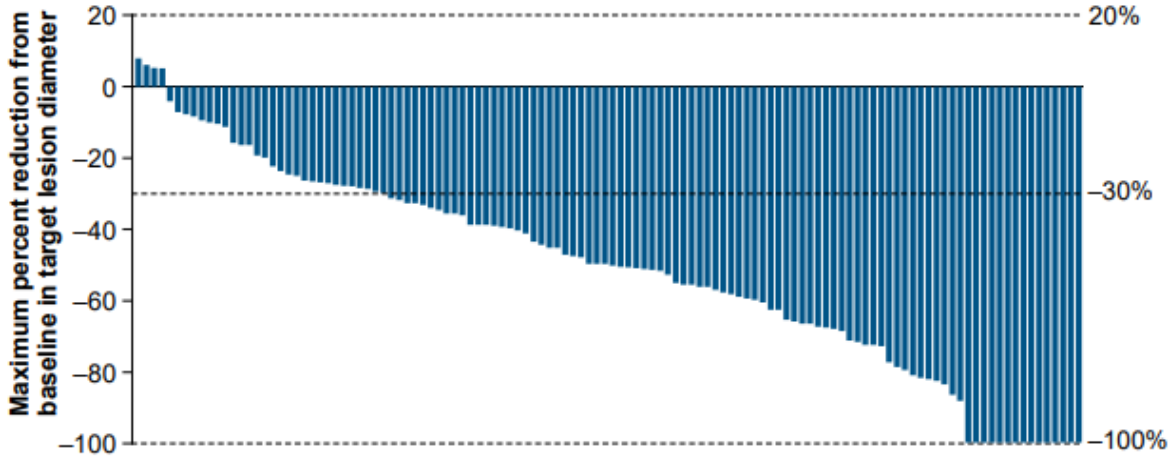
Waterfall plots presenting the maximum percentage reduction baseline in target lesion diameter for treatment-naïve patients and patients previously treated with chemotherapy (measurable disease population), are presented below in Figure 4 and Figure 5 respectively.

Figure 4: Tumour shrinkage in treatment-naïve patients



[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

Figure 5: Tumour shrinkage in patients with prior platinum-based chemotherapy



B.2.6.2 Secondary efficacy endpoints

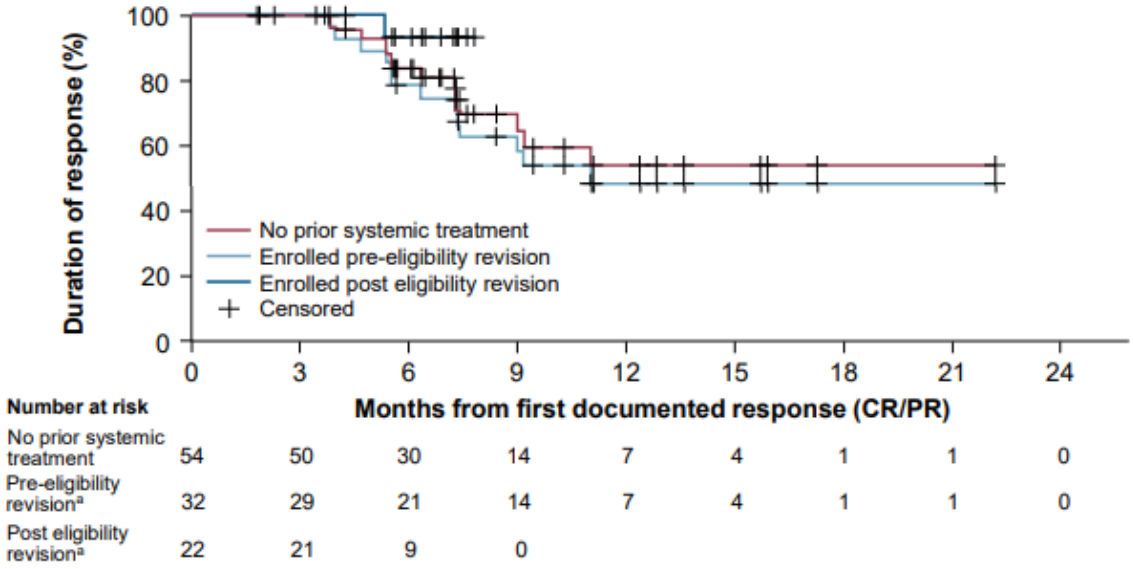
Duration of response

Measurable disease population

Among all 148 patients in the MDP with a confirmed tumour response, median DOR was 22.3 months (95% CI: 15.1, NR) with 67.6% of the responding patients censored. KM estimates for ongoing response were 84.0% (95% CI: 77.7, 90.3) at 6 months, 72.8% (95% CI: 64.8, 80.9) at 9 months, 63.2% (95% CI: 53.9, 72.6) at 12 months, and 53.7% (95% CI: 43.0, 64.3) at 18 months (67).

- *Treatment naïve subgroup*: among the 54 patients with a confirmed tumour response, median DOR was NR (95% CI: 9.0, NR) with 74.1% of the responding patients censored. KM estimates for ongoing response were 83.8% (95% CI: 72.8, 94.8) at 6 months, 69.9% (95% CI: 54.3, 85.5) at 9 months, and 53.9% (95% CI: 33.9, 74.0) at 12 months.

Figure 6: Duration of response in treatment-naïve patients



[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

- *Prior systemic treatment subgroup*: among the 94 patients with a confirmed tumour response, median DOR was 22.3 months (95% CI: 15.1, NR) with 63.8% of the responding patients censored. KM estimates for ongoing response were 84.0% (95% CI: 76.3, 91.7) at 6 months, 73.9% (95% CI: 64.4, 83.3) at 9 months, 66.2% (95% CI: 55.6, 76.8) at 12 months, and 55.3% (95% CI: 43.3, 67.3) at 18 months.

Figure 7: Duration of response in prior platinum-based chemotherapy

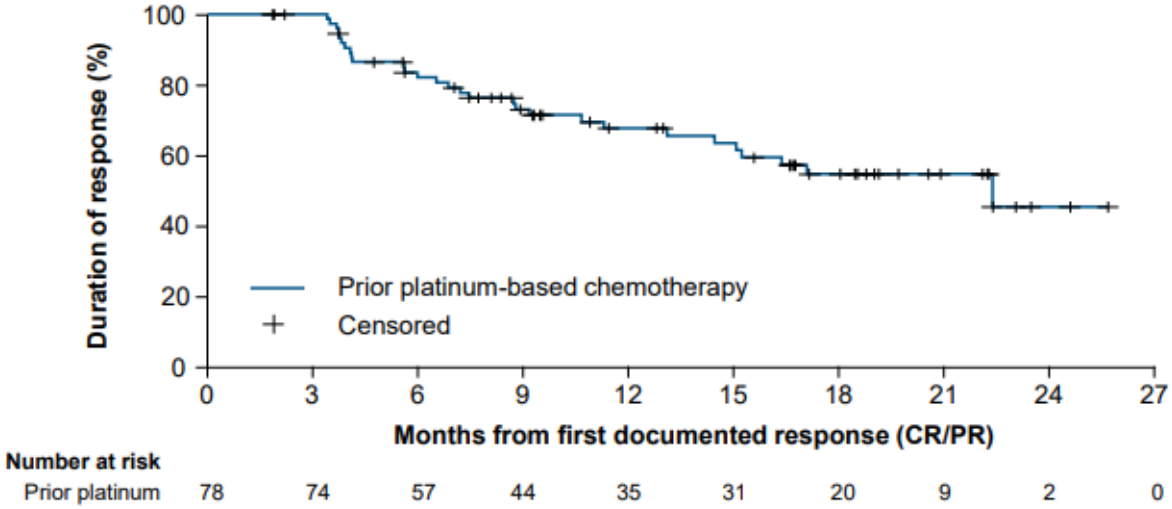


Table 14: DOR in patients with *RET* fusion–positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC N=216	All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
DOR, months (95% CI)	22.3 (15.1, NR)	NR (9.0, NR)	11.0 (7.4, NR)	NR (NR, NR)	22.3 (15.1, NR)	22.3 (15.1, NR)	NR (9.2, NR)

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.
CI, confidence interval; DOR, duration of response; NR, not reported
CCOD: 06 November 2020

Clinical benefit rate

Measurable disease population

In the overall MDP (n=216), CBR, representing the proportion of patients with SD duration ≥16 weeks or a confirmed response, was 76.9% (95% CI: 70.6, 82.3) (67).

- *Treatment-naïve subgroup* (n=68): CBR was 82.4% (95% CI: 71.2, 90.5)
- *Prior systemic treatment subgroup* (n=148): CBR was 74.3% (95% CI: 66.5, 81.1)

Table 15: CBR in patients with *RET* fusion–positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC N=216	All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
CBR, % (95% CI)	77 (71, 82)	82 (71, 91)	79 (64, 90)	88 (69, 98)	74 (67, 81)	74 (65, 81)	77 (55, 92)

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted
CR or PR or SD of ≥16 weeks.
CBR, clinical benefit rate; CI, confidence interval
CCOD: 06 November 2020

Disease control rate

Measurable disease population

DCR, or the proportion of patients with best overall response of SD or a confirmed response, was 91.7% (95% CI: 87.1, 95.0 in the overall MDP (n=216) (67).

- *Treatment-naïve subgroup* (n=68): DCR was 92.6% (95% CI: 83.7, 97.6)
- *Prior systemic treatment subgroup* (n=148): DCR was 91.2% (95% CI: 85.4, 95.2)

Table 16: DCR in patients with *RET* fusion–positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC N=216	All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
DCR, % (95% CI)	92 (87, 95)	93 (84, 98)	91 (78, 97)	96 (80, 100)	91 (85, 95)	91 (85, 96)	91 (71, 99)

CI, confidence interval; DCR, disease control rate
CCOD: 06 November 2020

Progression-free survival

PFS of patients with *RET* fusion–positive NSCLC treated at 400 mg QD is summarised for the unrestricted efficacy population (all patients in the safety population with *RET* fusion–positive NSCLC who were initiated with 400 mg pralsetinib regardless of date of initial dosing).

Unrestricted efficacy population

[redacted]. Overall, [redacted] patients in the unrestricted efficacy population had a median PFS of [redacted] months (95% CI: [redacted]). A

total of 175 patients [redacted]) in this population were censored for analysis and [redacted] patients ([redacted]) had a PFS event.

- *Treatment-naïve subgroup* (n=116): estimated median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored
- *Prior systemic treatment subgroup* (n=165): median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored

Table 17: PFS of patients with *RET* fusion–positive NSCLC in the unrestricted efficacy population and efficacy population

	Unrestricted Efficacy Population		
	All *RET* positive NSCLC [redacted]	**Prior Systemic Treatment** [redacted]	**Treatment Naïve** [redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Patients Censored, n (%)	[redacted]	[redacted]	[redacted]
PFS KM estimates, Months			
Median (95% CI[a])	[redacted]	[redacted]	[redacted]
PFS Rate, %			
3 months 95% CI	[redacted]	[redacted]	[redacted]
6 months 95% CI	[redacted]	[redacted]	[redacted]
9 months 95% CI	[redacted]	[redacted]	[redacted]
12 months 95% CI	[redacted]	[redacted]	[redacted]
18 months 95% CI	[redacted]	[redacted]	[redacted]
24 months 95% CI	[redacted]	[redacted]	[redacted]

CI, confidence interval; EMA, European Medicines Agency; KM, Kaplan–Meier; PFS, progression-free survival; NR, not reported; NSCLC, non-small cell lung carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours.

[a]The 95% CI is based on Greenwood formula.

CCOD: 06 November 2020

The Kaplan-Meier (KM) survival curve for PFS analyses in the unrestricted efficacy population is provided below.

Figure 8: KM survival curve of PFS in the Overall Unrestricted Efficacy Population

[redacted]

Figure 9: KM survival curve of PFS in the untreated subgroup of the unrestricted efficacy population

Figure 10: KM survival curve of PFS in the pre-treated subgroup of the unrestricted efficacy population

Overall survival

Overall survival of patients with *RET* fusion–positive NSCLC treated at 400 mg QD of pralsetinib is summarised for the unrestricted efficacy population.

Unrestricted efficacy population

[redacted]. Among all [redacted] patients in the unrestricted efficacy population, [redacted] Median follow-up was [redacted] months and [redacted] of patients were censored.

- *Treatment-naïve subgroup* ([redacted]): KM estimated OS rate was [redacted] at both 6 months and 9 months, [redacted] at 12 months and [redacted] at 18 months
- *Prior systemic treatment subgroup* ([redacted]): KM estimated OS rate was [redacted] at 6 months, [redacted] at 9 months, [redacted] at 12 months and [redacted] at 18 months

Table 18: OS of patients with *RET* fusion–positive NSCLC in the unrestricted efficacy population and efficacy population

Parameter	Unrestricted Efficacy Population		
	All *RET* positive NSCLC	Prior Systemic Treatment	Treatment Naïve
Deaths, n (%)[a]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
Overall follow-up time KM estimates[a], months			
Median (95% CI[b])	[redacted]	[redacted]	[redacted]
OS KM 3stimate, Months			
Median (95% CI)	[redacted]	[redacted]	[redacted]
OS Rate, n (%)			
3 months 95% CI	[redacted]	[redacted]	[redacted]
6 months 95% CI	[redacted]	[redacted]	[redacted]
9 months 95% CI	[redacted]	[redacted]	[redacted]
12 months 95% CI	[redacted]	[redacted]	[redacted]
18 months 95% CI	[redacted]	[redacted]	[redacted]
24 months 95% CI	[redacted]	[redacted]	[redacted]

CI, confidence interval; KM, Kaplan–Meier; NSCLC, non-small cell lung cancer; OS, overall survival.
[a]Overall follow-up time is based on reverse KM method.
[b]The 95% CI is based on Greenwood formula.
CCOD: 06 November 2020

The KM survival curve for OS analyses in the overall unrestricted efficacy population is provided below.

Figure 11: KM survival curve of OS in the overall unrestricted efficacy population

[redacted]

Figure 12: KM survival curve of OS in the untreated subgroup of the overall unrestricted efficacy population

[redacted]

Figure 13: KM survival curve of OS in the pre-treated subgroup of the overall unrestricted efficacy population

[redacted]

B.2.6.3 Exploratory and additional endpoints

CNS activity assessed by BICR

Pralsetinib penetrates the blood–brain barrier and is efficacious in brain metastases: an intracranial ORR rate of [redacted] was observed in ten patients with measurable CNS metastases at baseline in the response-evaluable population.

Note: there were no patients with measurable baseline CNS metastases in the treatment-naïve subgroup.

Table 19: CNS response in the response-evaluable population

	All *RET* positive NSCLC ([redacted])	Prior Platinum Treatment ([redacted])
ORR, n (%) 95% CI	[redacted]	[redacted]
Best overall response, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]
CBR, n (%) 95% CI	[redacted]	[redacted]
DCR, n (%) 95% CI	[redacted]	[redacted]

CBR, clinical benefit rate; CI, confidence interval; CNS, central nervous system; CR, complete response, DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

B.2.6.4 Patient-reported outcomes

The EORTC QLQ-C30 was completed by patients enrolled on or after protocol amendment 7 during Phase 2, where the starting dose for all patients was 400 mg QD (65).

Overall, the median (range) EORTC QLQ-C30 global health status score in patients with *RET* fusion–positive NSCLC was 83.0 (75 to 100) out of 100 possible points at the last assessment (Week 48), with minimal changes (≤16 points) from baseline observed at all time points over a duration of 48 weeks.

High mean and median scores have been reported for physical, role, emotional, cognitive, and social functioning indicating a high level of functioning, with minimal changes from baseline observed at all time points (mostly <10 points change from baseline. At baseline, patients reported low levels of clinical symptoms, which remained low with little changes throughout all time points. From baseline to last assessment, there was a tendency toward less pain and insomnia (change of ≤16 points) and toward more constipation (consistent with what was seen for AE reporting). Low mean and median scores were observed for the financial difficulties scale, with no relevant changes from baseline observed at all time points.

There were no clinically relevant differences in QoL results among the prior treatment subgroups of NSCLC patients.

B.2.7 Subgroup analysis

At the date of cut-off (06 November 2020), sub-group analyses were determined by *RET* genotype and by prior anticancer therapy.

ORR by RET Genotype

ORR results by *RET* genotype were evaluated in the prior platinum treatment subgroup in the efficacy population:

- Patients with *RET* fusion partner
- Patients with *RET* fusion partner
- Patients with other *RET* fusion partners

ORR by Prior Anticancer Therapy

ORR was determined by prior anticancer therapy both in the MDP and efficacy population.

Measurable Disease Population

Efficacy population:

- [redacted]
- [redacted]

B.2.8 Meta-analysis

No meta-analysis was conducted as only one single-arm clinical trial (ARROW) provides the clinical evidence for pralsetinib in this setting.

B.2.9 Indirect and mixed treatment comparisons

ARROW was a single-arm study and as such provided no direct estimation of treatment effect for pralsetinib. In order to inform decision making for the current appraisal, indirect treatment comparisons were required between pralsetinib and the untreated and pre-treated comparators outlined in Section B.1.1. The remainder of this section outlines the approach taken to inform the indirect treatment comparison.

B.2.9.1 SLR and MAIC in *RET* fusion-positive population

A systematic literature review (SLR) with broad inclusion criteria was conducted in order to identify published literature in *RET* fusion-positive advanced NSCLC patient populations with a view to conducting a matching adjusted indirect comparison (MAIC) to inform decision making (68). Details of this SLR are presented in Appendix D.

The available clinical evidence for *RET* fusion-positive advanced NSCLC patient populations identified in the SLR was sparse. No studies were identified that corresponded to the comparators identified in Section B.1.1, so a MAIC in this patient population was not a feasible approach to estimating an indirect treatment comparison for the current appraisal.

B.2.9.2 Flatiron Health data set comparison in *RET* fusion-positive population

Objective

Given the lack of available evidence in the published literature on *RET* fusion-positive advanced NSCLC patient populations, Roche sought to use available real world evidence in order to inform an indirect treatment comparison. The use of real world data to address evidence gaps is seen by NICE as key pillar of their future strategic ambition across the next 5 years. (69) The Flatiron database is a United States (US) nationwide, demographically and geographical diverse observational database derived from electronic health record data. The database includes data from over 280 cancer clinics (~800 sites of care) representing more than 2.2 million active U.S. cancer patients available for analysis. The indirect treatment comparison outlined in this section aimed to compare OS, PFS, and TTD between *RET*-

fusion positive NSCLC patients treated with pralsetinib from the ARROW clinical trial versus best available therapy for *RET* fusion-positive advanced NSCLC in the Flatiron database for untreated and pre-treated settings (70).

Methodology

For this study, the records of patients diagnosed with NSCLC in the US were extracted from the Flatiron electronic health record-derived de-identified database. The source population was the overall population reported in the Flatiron electronic health record database and managed in at least one of the US oncology clinics taking part in the Flatiron Health network from 01 January 2011 onwards with at least two visits in the Flatiron system. The Flatiron Health and Foundation Medicine (FMI) NSCLC Clinico-Genomic database (CGDB) was used for the study. The NSCLC CGDB includes patients with ≥2 visits in the Flatiron database on or after 1 January 2011 who underwent comprehensive genomic profiling by FMI on or after the initial diagnosis date on a sample that was collected no earlier than 30 days prior to the diagnosis date. The Flatiron Health patients were eligible for this study if they were diagnosed with locally advanced or metastatic *RET*-fusion positive NSCLC between 1 January 2011 and 30 June 2020 and initiated first-line or second-line therapy at a Flatiron Health clinic. Patients in the comparator arm were not restricted on treatments and the comparator arm consisted of best available therapy.

Pralsetinib was modelled using ARROW data with the efficacy population from the 06 November 2020 data cut. Inverse probability of treatment weighting (IPTW) was considered, however, due to sample size limitations, there was no way to improve the balance between populations. Therefore, unadjusted analyses were conducted.

Results

After application of study eligibility criteria, 10 untreated and six pre-treated participants were identified in the Flatiron Health cohort. Best available therapy consisted of pembrolizumab + chemotherapy ([redacted]), platinum-based chemotherapy ([redacted]), immunotherapy monotherapy ([redacted]) and other ([redacted]). Given the sample size limitations, this patient population was not considered suitable to inform decision making. In the untreated analysis, results favoured pralsetinib over best available therapy (OS HR [redacted], 95% CI [redacted]; PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]). However, due to the test being underpowered, results were not statistically significant and CIs crossed one.

Discussion

The analysis outlined in this section (B.2.9.2) is suggestive of potential benefits of pralsetinib. Results suggested that pralsetinib did not demonstrate statistically significantly

lower OS, PFS or TTD against best available therapy in the untreated setting. However, this analysis faced significant limitations due to small sample size well below what is considered appropriate to inform decision making and that the comparator arm represents best available care and not individual treatment comparisons against comparators identified in Section B.1.1. Therefore, this analysis was not considered robust enough to inform decision making in the current appraisal.

B.2.9.3 Chart review in *RET* fusion-positive population

As outlined in Section B.2.9.1-2, both the published literature and real world evidence from the Flatiron Health dataset did not provide a suitable evidence base to generate comparative evidence to inform decision making for the current submission. Therefore, Roche commenced a chart review which involves hand searching hospital records across Europe in order to identify a historical cohort of *RET* fusion-positive advanced NSCLC patients and their associated outcomes to generate comparative effectiveness data. The chart review is currently ongoing and estimated to be completed in August 2021. If available, Roche will aim to provide this comparative analysis as part of the response to clarification questions.

B.2.9.4 SLR naïve and propensity scoring comparison in WT population

Objective

As outlined in Sections B.2.9.1-3, an indirect treatment comparison in a *RET* fusion-positive patient population was not feasible to inform decision making at this stage of the current submission. There is currently no evidence in the available published literature to suggest a prognostic value for *RET* fusion-positive status compared to wild-type (WT, that is, patients with tumours without a gene mutation or rearrangement or unknown mutation status) advanced NSCLC patients after controlling for baseline patient characteristics (2). This was corroborated by the clinical expert in the selpercatinib appraisal who stated that the effect of RET fusion on treatment effectiveness for people with advanced NSCLC is unknown (71). Therefore, in the absence of available evidence to inform a *RET* fusion-positive comparison, an approach was taken to conduct an indirect treatment comparison of pralsetinib data from ARROW against a WT population from the available literature. This approach was discussed and approved as part of the Decision Problem Meeting (19th April 2021) with NICE and the ERG.

Compared to WT advanced NSCLC patients, *RET* fusion-positive patients demonstrate differing patient characteristics. *RET* fusion-positive patients tend to be non-squamous, younger, and are more likely to have never smoked compared to WT patients. Given the differences in baseline characteristics between *RET* fusion-positive and WT patient

populations, it was preferable that in any indirect treatment comparison, adjustment was done so that patient characteristics between pralsetinib and comparators were comparable so as not to bias results. Further, it is preferable that the WT population should be adjusted to reflect the baseline characteristics of the *RET* fusion population to ensure the indirect treatment comparison represents a *RET* vs (adjusted) *RET* comparison so that the patient population is aligned to the scope of this submission. Individual patient level data is required for patient characteristic adjustment. Therefore, indirect treatment comparison approaches with individual patient level data in the WT comparator arm are is preferred so that characteristics can be matched to ARROW and inferences be drawn from a target *RET* fusion-positive patient population. In the absence of patient-level data, however, only naïve comparisons can be performed.

Roche expanded the scope of the SLR in Section B.2.9.1 to identify RCTs conducted in patients with WT NSCLC treated in either the untreated or pre-treated setting (72). The principal objective of the SLR was to identify appropriate candidate RCTs examining relevant comparator interventions (as defined by comparators in Section B.1.1) in patients with WT advanced NSCLC with a view to using results to inform an indirect treatment comparison against pralsetinib to inform the current appraisal.

Methodology

SLR

Full details of the SLR including search strategy, search terms and study selection are provided in Appendix L.

Pralsetinib was modelled using ARROW data with the unrestricted efficacy population from the 06 November 2020 data cut.

Note that in the absence of individual patient data for comparator interventions of interest, unanchored MAIC analyses represent a potential methodology for generating estimates of relative treatment effect. However, this methodology was not relevant for the current appraisal, primarily due to differences in patient characteristics between NSCLC *RET* fusion-positive and WT populations. The lack of overlap in the patient populations means that any adjustments would likely results in a very small effective sample size (ESS) for pralsetinib. Additionally, in the absence of individual patient data for the comparator study, a MAIC analysis only provides an estimate of the treatment effect in the comparator population as the target population, by weighting the ARROW population to match the comparator study characteristics, which may not be the appropriate cohort to inform decision making.

Therefore, two approaches to comparative analyses were conducted based on the WT SLR (Appendix L) - propensity score analysis and naïve comparisons.

Propensity scoring with average treatment-effect on treated (ATT) estimand

Roche-sponsored trials conducted in WT NSCLC that included treatment arms of relevant comparators represents the most appropriate data to allow for comparative analyses of pralsetinib with comparators where individual patient data were available-allowing for statistical matching techniques to estimate the effect of treatment by accounting for covariates which may be considered to be prognostic factors or treatment-effect modifiers. The use of individual patient data from both ARROW and a comparator arm of interest allows for propensity score analyses using IPTW methodology.

Propensity scoring is a recognised technique used in controlling for selection biases when combining multiple sources of non-randomised evidence. Propensity scores can be used as weights to account for selection assignment differences between treatment and comparison groups. The propensity scoring approach is based on methodology recommended by the NICE Decision Support Unit guidance (TSD 17) (73). The standard IPTW approach, resulting in an average treatment effect (ATE) estimand, uses the propensity score function (probability of treatment assignment is considered to be a function of a set of observable covariates), and assigns more weight to the observations which appear in one group but have a small probability of being found in that group. Weights are then estimated as the inverse of the propensity score, and a weighted outcome analysis is then performed. Alternatively, when the treatment populations are very different – which is generally the case when comparing *RET*-fusion positive and WT populations – it is more appropriate to estimate ATT estimands by assigning a weigh of 1 to the ARROW target population and [propensity score]/(1-[propensity score]) to the comparator population. That means that patients enrolled in the comparator study are re-weighted to match the characteristics of ARROW patients, and estimates represent how patients similar to those enrolled in ARROW would have fared if they had been treated with the comparator arm instead of pralsetinib.

In order to conduct a propensity scoring analysis, it is necessary to identify a set of covariates to include in the statistical model, which are believed to be either prognostic of outcomes or potential treatment-effect modifiers; these factors are used to predict the probability of exposure and is considered a critical step of propensity scoring analysis. In the current analysis, age, gender, race, presence of CNS metastases, ECOG PS, smoking status and histology were considered.

In order to estimate the relative treatment effect, a Cox regression model was then fitted to the pooled individual patient data utilising the weights obtained from the propensity scoring

analyses (ATT) to estimate the weighted treatment-effect between pralsetinib and the comparator under investigation in a population that has characteristics similar to ARROW.

Naïve comparisons

In the absence of individual patient data for comparator interventions of interest, naive comparisons were conducted. Naïve comparisons were conducted to compare outcomes (without performing any adjustment) and to estimate a treatment-effect between pralsetinib and each comparator of interest. Only published aggregate-level data were reported for all of the comparator studies. Data for OS and PFS were recreated from published Kaplan-Meier curves using an algorithm developed by Guyot 2012 (74). Virtual individual patient data were then estimated by generating survival data for each comparator of interest. A Cox regression model was then fitted to the individual patient data from ARROW and the recreated individual patient data from each comparator study to estimate a naïve hazard ratio (HR) between pralsetinib vs the comparator under investigation, with uncertainty around the treatment-effect presented as a 95% CI. No adjustment was made for any differences between study populations.

Stepwise approach for selecting comparative analysis

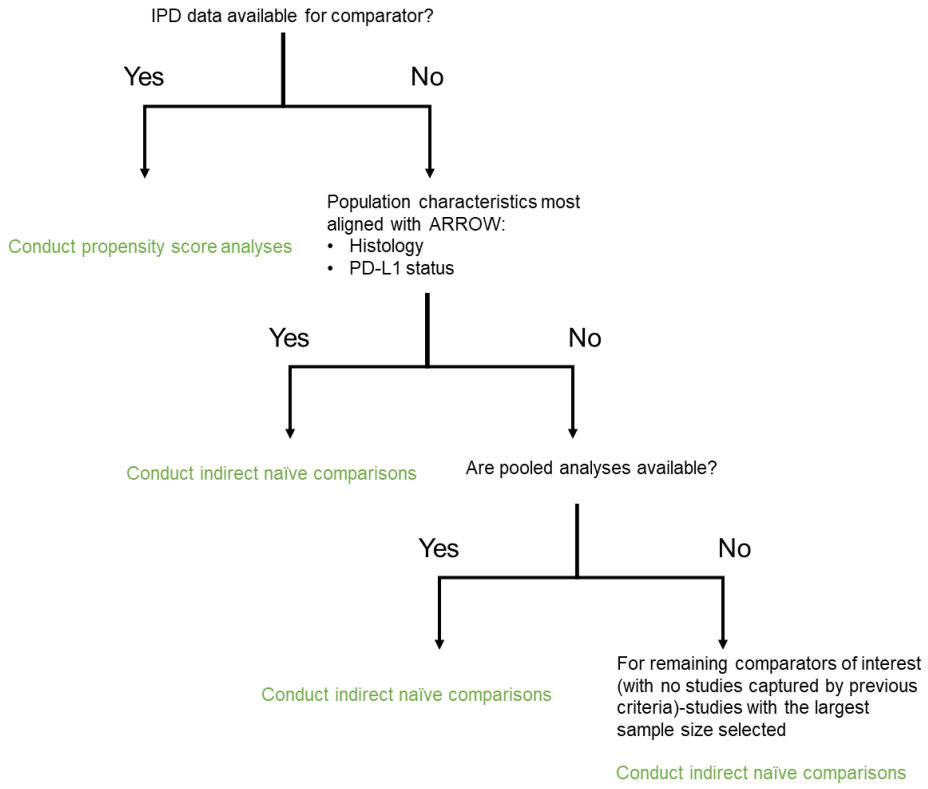
The availability of individual patient data for comparator trials would allow for the most robust comparison of relevant comparators with pralsetinib as it would allow for propensity score analyses. A stepwise approach was undertaken to select the most appropriate RCT for the interventions of interest to be used in the comparative analyses Figure 14:

1. Where individual patient data were available from Roche sponsored trials, these trials were selected for propensity score analyses

For the remaining comparators of interest, naïve comparisons were conducted with relevant comparator studies selected via the following hierarchy:

2. The enrolled population was aligned with ARROW in terms of histology and PD-L1 status
3. Pooled analyses available
4. The study with the largest number of patients (or only available study) was selected.

Figure 14 Overview of methodology for the selection of studies for the comparative analyses



Results

Table 20 summarises the results of the indirect treatment comparison with the chosen comparative analysis for each submission comparator, the literature source used from the SLR and the respective hazard ratios against pralsetinib OS and PFS. One Roche-sponsored study was available (OAK) for docetaxel monotherapy. This included individual patient data and therefore a propensity scoring analysis was conducted. For all other submission comparators, a naïve treatment comparison was used. Across both untreated and pre-treated populations, pralsetinib represented a statistically significant improvement in OS and PFS for patients compared to all comparators.

Table 20: Hazard ratios vs. pralsetinib used in the WT SLR (Appendix L) indirect treatment comparison and comparators sources

Treatment	Outcome	Population	Pralsetinib	Comparator		Method of analysis used	Pralsetinib vs comparator HR (95% CI)
			N	Study	N		
Pembrolizumab + pemetrexed + chemotherapy	OS	Untreated	[redacted]	KEYNOTE-189 (75)	299	Naïve (largest sample size)	
	PFS						
Pembrolizumab monotherapy	OS	Untreated	[redacted]	KEYNOTE-042; PD-L1 ≥50% (76)	410	Naïve (largest sample size)	
	PFS						
Docetaxel monotherapy	OS	Pre-treated	[redacted]	OAK trial (77)	Unadjusted: 510 Adjusted: 142	Propensity scoring	
	PFS						
Docetaxel + nintedanib	OS	Pre-treated	[redacted]	LUME-Lung 1 (57)	655	Naïve (largest sample size)	
	PFS				565		
Pemetrexed + carboplatin	OS	Pre-treated	[redacted]	GOIRC 02-2006 + NVALT7 (78)	238	Naïve (pooled analysis)	
	PFS				119		

Where hazard ratio <1 favours pralsetinib. For pemetrexed + carboplatin, PFS was based on GOIRC 02-2006 data in the absence of reported Kaplan-Meier curve for NVALT7. For the comparison to docetaxel monotherapy, equalising of study populations reduced the pre-treated pralsetinib patient population from 165 to 144
HR, hazard ratio, PFS, progression-free survival; OS, overall survival; SLR, systematic literature review, WT, wild-type

Figure 15 and Figure 16 demonstrate the Kaplan-Meier curves for pralsetinib compared to pembrolizumab + pemetrexed + chemotherapy in the untreated setting. However, due to differences in characteristics between the studies such as the proportion of subjects who have never smoked (21% in KEYNOTE 042 and [redacted] in ARROW (Table 8)) and being female (31% in KEYNOTE 042 and [redacted] in ARROW (Table 8)) results should be interpreted with caution.

Figure 15: Kaplan-Meier estimates using naïve comparison for OS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. KEYNOTE-189)

[redacted]

Figure 16: Kaplan-Meier estimates using naïve comparison for PFS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. KEYNOTE-189)

[redacted]

Figure 17 and Figure 18 demonstrate the Kaplan-Meier curves for pralsetinib compared to pembrolizumab monotherapy in the untreated setting. However, due to differences in characteristics between the studies such as the proportion of subjects who have never smoked (12% in KEYNOTE 189 and [redacted] in ARROW (Table 8)) and being female (38% in KEYNOTE 042 and [redacted] in ARROW (Table 8)) results should be interpreted with caution.

Figure 17: Kaplan-Meier estimates using naïve comparison for OS comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. KEYNOTE-042)

[redacted]

Figure 18: Kaplan-Meier estimates using naïve comparison for PFS comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. KEYNOTE-042)

[redacted]

Figure 19 and Figure 20 demonstrate the Kaplan-Meier curves for pralsetinib compared to docetaxel monotherapy in the pre-treated setting.

Figure 19: Kaplan-Meier estimates using propensity scoring for OS comparing pralsetinib with docetaxel monotherapy in pre-treated setting (ARROW vs. OAK)

[redacted]

Figure 20: Kaplan-Meier estimates using propensity scoring for PFS comparing pralsetinib with docetaxel monotherapy in pre-treated setting (ARROW vs. OAK)

[redacted]

Figure 21 and Figure 22 demonstrate the Kaplan-Meier curves for pralsetinib compared to docetaxel + nintedanib in the pre-treated setting.

Figure 21: Kaplan-Meier estimates using naïve comparison for OS comparing pralsetinib with docetaxel monotherapy in pre-treated setting (ARROW vs. LUME-Lung 1)

[redacted]

Figure 22: Kaplan-Meier estimates using naïve comparison for PFS comparing pralsetinib with docetaxel monotherapy in pre-treated setting (ARROW vs. LUME-Lung 1)

[redacted]

Figure 23 and Figure 24 demonstrate the Kaplan-Meier curves for pralsetinib compared to pemetrexed + carboplatin in the pre-treated setting.

Figure 23: Kaplan-Meier estimates using naïve comparison for OS comparing pralsetinib with pemetrexed + carboplatin in pre-treated setting (ARROW vs. GOIRC 02-2006 + NVALT7)

[redacted]

Figure 24: Kaplan-Meier estimates using naïve comparison for PFS comparing pralsetinib with pemetrexed + carboplatin in pre-treated setting (ARROW vs. GOIRC 02-2006 + NVALT7)

[redacted]

Discussion

The SLR was able to inform a comparative analysis for pralsetinib against submission comparators in a WT patient population in order to inform an estimate of treatment effect. Across the studies identified in the SLR, the sample sizes in the comparator populations was large (n=119-655). Results suggest that pralsetinib demonstrates statistically significant clinical outcomes across OS, PFS and TTD against all comparators included in the analysis.

In the one propensity scoring analysis conducted (pralsetinib vs docetaxel monotherapy in OAK), the weighted results are nearly identical to the unadjusted results, which suggests that the weighting has not had a notable impact on the treatment-effect for patients who have received prior systemic therapy in terms of OS or PFS prospects.

It was considered clinically implausible that for PFS, docetaxel + nintedanib would have a lower hazard ratio vs. pralsetinib than docetaxel monotherapy. This would imply a negative treatment effect of the addition of nintedanib. Given the docetaxel monotherapy used a propensity scoring analysis and was considered a more robust analysis, an assumption was made to assume the PFS of docetaxel + nintedanib was equivalent to docetaxel monotherapy (Section B.2.9.7).

The WT SLR (Appendix L) contains some limitations:

- Reflecting on the lack of scientific data regarding the prognostic value of *RET* status, and due to the paucity of available evidence in *RET* fusion-positive patients, a WT patient population was used in comparator arms of the indirect treatment comparison. IPTW adjustments were conducted to account for differences in important baseline characteristics where possible. There is no available evidence to demonstrate a prognostic effect of RET fusion status after weighting for patient characteristics (2, 71).
- Individual patient level data was available for the indirect treatment comparison against docetaxel monotherapy. However, for comparisons against the other comparators, no individual patient data was available and naïve comparisons were conducted. Naïve comparisons are limited in that comparator arms are not adjusted to match characteristics of a *RET* fusion-positive patient population. However, given the minimal impact of adjustment observed for the propensity scoring, it may be possible that naïve comparisons may be a good estimator of the true treatment effect.
- It is worth noting that for the pre-treated analysis, ARROW patients have received 1 or more prior systemic therapies (2L+) whereas in the LUME-Lung 1 and GOIRC 02-2006 + NVALT7 trials, patients received only 1 prior treatment, and patients in the OAK trial were exposed to mostly 1 previous therapy. This may bias the treatment effect against pralsetinib as it is reasonable to assume that patients on later lines may fare worse than earlier-line patients.

B.2.9.5 Flatiron Health data set comparison in WT population

Objective

As detail in Section B.2.9.4, indirect treatment comparison approaches with individual patient level data in the comparator arm are preferred so that the WT population can be adjusted to reflect the baseline characteristics of the *RET* fusion-positive population to ensure the indirect treatment comparison represents a *RET* vs (adjusted) *RET* comparison so that the patient population is aligned to the scope of this submission. In the WT SLR (Section B.2.9.4, Appendix L) individual patient data was only available for the docetaxel monotherapy comparison. The Flatiron database contains individual patient data to facilitate IPTW. For comparators where no individual patient data was available in the WT SLT (Section B.2.9.4, Appendix L), Roche sought to use available real world evidence from the Flatiron database (Section B.2.9.2) in order to inform an indirect treatment comparison. The use of real world data to address evidence gaps is seen by NICE as key pillar of their future strategic ambition across the next 5 years. (69) The indirect treatment comparison outlined

in this section aimed to compare OS, PFS, and TTD between *RET*-fusion positive NSCLC patients treated with pralsetinib from the ARROW clinical trial versus WT patient populations for all submission comparators identified in Section B.1.1 (barring docetaxel where propensity scoring was able to be conducted n Section B.2.9.4) in the Flatiron database for untreated and pre-treated settings (79).

Methodology

Pralsetinib was modelled using ARROW data with the unrestricted efficacy population from the 06 November 2020 data cut.

The records of patients diagnosed with NSCLC in the US were extracted from the Flatiron EHR-derived de-identified database. The source population was the overall population reported in the EHR and managed in at least one of the U.S. oncology clinics taking part in the Flatiron Health network from 1 January 2011 onwards with at least two visits in the Flatiron system. The Flatiron Health patients were eligible for this study if they were from the Enhanced Data Mart (EDM) database, diagnosed with locally advanced or metastatic NSCLC between 1 January 2011 and 31 March 2020 and initiated 1L or 2L therapy at a Flatiron Health clinic between 2017 and 2019 (to be contemporary to ARROW).

In accordance with best practices, patients with >90-day gap between date of diagnosis and first visit/medication administration were excluded (80). To account for the Covid-19 pandemic, patients were censored on 1 March 2020. All eligible patients were required to have at least 6 months of potential follow-up (i.e. treatment initiation date no later than 1 September 2019).

Key inclusion and exclusion criteria are presented below. For the Flatiron EDM data, “last follow-up” is defined as the date of the last available visit, lab, treatment, or medication administration (last electronic health record activity). Patients in the EDM were followed up until a cut-off date of 31st March 2020 in order to account for the COVID-19 pandemic.

Note that some patients in the EDM may be *RET* fusion-positive, however since genetic testing results are not sufficiently available, it would be more reasonable to assume that the EDM cohort mostly consists of *RET*- patients since oncogenic *RET* fusions have been identified in 1-2% of NSCLC (20-22).

Inclusion criteria:

- Patients must have unresectable locally advanced or metastatic NSCLC
    - ARROW patients must have a *RET*-fusion positive tissue sample
- Patient has an ECOG of 0 or 1

- The ARROW data has at most one subject with ECOG > 1. Thus, if EDM patients with ECOG > 1 are included, the non-overlap between the two datasets becomes an issue that cannot be solved by statistical weighting methods since we can only adjust for ECOG values common in both arms
- Subjects in the EDM database must have a line start date that falls between 2017 and 2019 (to be in line with the time frame of the ARROW trial)
- Histology must be non-squamous
    - For each comparison, the ARROW data has a handful of patients with squamous histology

Exclusion criteria:

- For EDM, patients with > 90-day gap between advanced diagnosis and first visit or medication administration were excluded in accordance with best practices
- Patients in the EDM must not have had pralsetinib or selpercatinib or clinical study drugs in any line
- Patient has another known driver mutation (EGFR, ALK, ROS1 or BRAF) at index date
- Index date less than 6 months prior to the EDM cut-off date
    - Patients that die within 6 months are included
- For Stage at initial diagnosis and Smoking status, patients must not have either missing entries or have entries labelled 'Not reported'.

Baseline characteristics captured for both the ARROW trial data and the EDM database that are explicitly adjusted for in the analyses include age, sex, smoking status, ECOG, time from initial diagnosis to first dose, stage at diagnosis and race. Metastases, sum of total metastases, brain/CNS metastases and liver metastases are also presented. Note that there are limitations for the variables involving metastases as the under-recording of these variables is a suspected limitation of the EDM database. Thus, achieving balance with respect to this variable was not a primary goal.

IPTW is a well-established method for mitigating bias due to measured confounders when estimating treatment effects in non-randomized settings (Williamson et al., 2012). The data for the ARROW pralsetinib arm and EDM comparator arm were pooled. A logistic regression propensity score model was estimated by regressing a pralsetinib treatment indicator on baseline covariates. Propensity scores were calculated for each patient using the fitted values from the propensity score model. IPTW weights for the ATT estimand were computed by assigning each patient in the pralsetinib arm a weight of 1 and each patient in the comparator arm a weight of [propensity score] / (1 – [propensity score]). The effective

sample size was calculated by taking the square of the sum of all weights divided by the summation of each of the weights squared (Kish, 1995). Subjects with a weight exceeding three were trimmed. The use of a fixed threshold was motivated by the observation that there were no scenarios where a large number of patients had large weights. All results presented for the IPTW analysis were produced after trimming subjects with large weights (Lee et al., 2011; Potter, 1993). Next, IPTW-weighted Cox proportional hazards (PH) regression models were used to estimate hazard ratios (HR) between the pralsetinib and comparator arms and 95% confidence intervals (95% CIs) were computed using robust standard errors. Sensitivity analysis using matching instead of IPTW was also conducted and is presented in the SLR report.

Results

The Flatiron database provided sufficient patient populations to conduct untreated comparisons against pembrolizumab + pemetrexed + carboplatin (where carboplatin was assumed to represent chemotherapy in UK clinical practice) and pembrolizumab monotherapy. In the pre-treated setting, the comparison against docetaxel + nintedanib was not feasible as this is not an approved treatment regimen in the US, whilst the sample size for platinum doublet chemotherapy (n=177) and pralsetinib (n=67) was too low to equalise large patient differences across datasets resulting in poor population matching, with only time since diagnosis achieving adequate balance (SMD<0.1), and unreliable results.

For the pralsetinib patient population from ARROW in the untreated comparisons (n= 116), seven patients were removed from the analysis to align with the Flatiron database eligibility criteria (i.e., ECOG PS 2 n=1, smoking history not reported n=3, stage not reported n=2, squamous n=1), resulting in 109 ARROW patients used in the analysis.

Untreated pembrolizumab + pemetrexed + chemotherapy

Table 21 displays the baseline characteristics for pralsetinib and the primary comparator, pembrolizumab + pemetrexed + chemotherapy, before and after the IPTW (ATT) adjustment. Following IPTW, balance was achieved among the matching covariates. The metastases-related variables are highly imbalanced, though these are suspected to be unreliable due to under recording in the Flatiron EDM database.

Table 21: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given pembrolizumab + pemetrexed + chemotherapy in untreated setting without and with adjustment

		Without adjustment			With adjustment			Adjusted
	Level	Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	
n		[redacted]	[redacted]					
Age (%)	< 65	[redacted]	[redacted]	0.4	[redacted]	[redacted]	0.015	Y
	≥ 65	[redacted]	[redacted]		[redacted]	[redacted]		
Sex (%)	F	[redacted]	[redacted]	0.187	[redacted]	[redacted]	0.007	Y
	M	[redacted]	[redacted]		[redacted]	[redacted]		
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	1.25	[redacted]	[redacted]	0.017	Y
	No history of smoking	[redacted]	[redacted]		[redacted]	[redacted]		
ECOG (%)	0	[redacted]	[redacted]	0.191	[redacted]	[redacted]	0.037	Y
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.148	[redacted]	[redacted]	0.042	Y
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.013	[redacted]	[redacted]	0.028	Y
	STAGE IV	[redacted]	[redacted]		[redacted]	[redacted]		
Race (%)	White	[redacted]	[redacted]	0.573	[redacted]	[redacted]	0.061	Y
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
	Unknown	[redacted]	[redacted]		[redacted]	[redacted]		
Sum of total metastases (median [IQR])		[redacted]	[redacted]	1.534	[redacted]	[redacted]	1.529	N
Metastases (%)	Isolated brain/CNS site	[redacted]	[redacted]	1.61	[redacted]	[redacted]	1.672	N
	None	[redacted]	[redacted]		[redacted]	[redacted]		
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
Brain/CNS metastasis only (%)	0	[redacted]	[redacted]	0.333	[redacted]	[redacted]	0.383	N
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Liver metastasis only (%)	0	[redacted]	[redacted]	0.25	[redacted]	[redacted]	0.32	N
	1	[redacted]	[redacted]		[redacted]	[redacted]		

Pralsetinib demonstrates a statistically significant improvement in OS (HR [redacted], 95% CI [redacted], [redacted]) compared to the primary comparator pembrolizumab + pemetrexed + chemotherapy. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]).

Figure 25-Figure 27 demonstrate the Kaplan-Meier curves for pralsetinib compared to pembrolizumab + pemetrexed + chemotherapy and the impact of the IPTW (ATT) adjustment.

Figure 25: Kaplan-Meier estimates using IPTW for OS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

[redacted]

Figure 26: Kaplan-Meier estimates using IPTW for PFS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Figure 27: Kaplan-Meier estimates using IPTW for TTD comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Untreated pembrolizumab monotherapy

Table **22** displays the baseline characteristics for pralsetinib and pembrolizumab monotherapy before and after the IPTW (ATT) adjustment. Following IPTW, balance was achieved for the majority of matching covariates though age, smoking history and race remain imbalanced. The metastases-related variables are highly imbalanced, though these are suspected to be unreliable due to under recording in the Flatiron EDM database.

Pralsetinib demonstrates a statistically significant improvement in OS (HR [redacted], 95% CI [redacted], [redacted]) compared to pembrolizumab monotherapy. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]).

Figure 28-Figure 30 demonstrate the Kaplan-Meier curves for pralsetinib compared to pembrolizumab + pemetrexed + chemotherapy and the impact of the IPTW adjustment (ATT).

Table 22: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given pembrolizumab monotherapy in untreated setting without and with adjustment

		Without adjustment			With adjustment			Adjusted
	Level	Pembrolizumab monotherapy	Pralsetinib	SMD	Pembrolizumab monotherapy	Pralsetinib	SMD	
n								
Age (%)	< 65			0.4			0.23	Y
	≥ 65							
Sex (%)	F			0.187			0.072	Y
	M							
Smoking history at baseline (%)	History of smoking			1.25			0.192	Y
	No history of smoking							
ECOG (%)	0			0.191			0.075	Y
	1							
Time from initial diagnosis to first dose (months) (median [IQR])				0.148			0.078	Y
Stage at initial diagnosis (%)	STAGE I, II, or III			0.013			0.038	Y
	STAGE IV							
Race (%)	White			0.573			0.199	Y
	Other							
	Unknown							
Sum of total metastases (median [IQR])				1.534			1.728	N
Metastases (%)	Isolated brain/CNS site			1.61			1.872	N
	None							
	Other							
Brain/CNS metastasis only (%)	0			0.333			0.241	N
	1							
Liver metastasis only (%)	0			0.25			0.398	N
	1							

Figure 28: Kaplan-Meier estimates using IPTW for OS comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Figure 29: Kaplan-Meier estimates using IPTW for PFS comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Figure 30: Kaplan-Meier estimates using IPTW for TTD comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Table 23: Summary of hazard ratios vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR	PFS HR	TTD HR	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)

Where hazard ratio <1 favours pralsetinib
ATT, average treatment-effect on treated; EDM, enhanced data mart; HR, hazard ratio, PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Discussion

The Flatiron indirect treatment comparison was able to inform a comparative effectiveness analysis for pralsetinib against pembrolizumab + pemetrexed + chemotherapy (primary comparator) and pembrolizumab monotherapy in a real-world US WT patient population. Across the Flatiron EDM database, following harmonization of eligibility criteria, the sample sizes in the comparator populations were large (n=686-1270). Results suggest that pralsetinib demonstrates statistically significant effectiveness across OS, PFS and TTD against the two comparators included in the analysis.

As individual patient data was available from the Flatiron database, comparator arms could be adjusted using IPTW. The IPTW adjustment for the pembrolizumab + pemetrexed + chemotherapy arm lead to a slight improvement in OS and has very minimal impact on PFS and TTD.

The IPTW adjustment for the pembrolizumab monotherapy arm lead to a slight decrease in OS, and more substantial decrease in PFS and TTD in the comparator arm. This result is to be expected given the relative ineffectiveness of pembrolizumab monotherapy of treating patients with the characteristics of *RET* fusion-positive patients. This is supported by the available published literature and was validated by clinical expert opinion (51-53). The likely key driver in the downwards pressure of this adjustment is the smoking history variable. In the pembrolizumab monotherapy patient population, [redacted] of patients had a history of smoking (vs. [redacted] in pralsetinib patient population). Evidence suggests that pembrolizumab monotherapy has lower efficacy in treating patients without a history of smoking (81). Therefore, by matching to a higher prevalence of non-smokers in ARROW, the IPTW adjustment has up-weighted non-smokers on pembrolizumab monotherapy resulting in widening the treatment effect of pralsetinib. This reflects likely outcomes in UK clinical practice where pralsetinib is anticipated to demonstrate a large treatment effect on survival in the subset of patients with no history of smoking compared to pembrolizumab monotherapy.

The Flatiron analysis was validated by clinical experts in an advisory board. Clinical experts stated that the treatment effects calculated were representative of likely treatment outcomes of treatment with pralsetinib in UK clinical practice.

The Flatiron indirect treatment comparison contains some limitations:

- Reflecting on the lack of scientific data regarding the prognostic value of *RET* status, and due to the paucity of available evidence in *RET* fusion-positive patients, a WT patient population was used in comparator arms of the indirect treatment comparison. IPTW adjustments were conducted to account for differences in important baseline characteristics where possible. There is no available evidence to demonstrate a prognostic effect of RET fusion status after weighting for patient characteristics (2, 71).
- Given the availability of treatments in the US based Flatiron real-world evidence dataset, comparisons were only possible against pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy in the untreated setting. These two represent both comparators in the untreated patient population. The Flatiron database was not suitable to conduct decision-grade comparisons against docetaxel + nintedanib or platinum-based chemotherapy +/- pemetrexed in the pre-treated population.
- There is an imbalance between the patient populations regarding metastases variables. The recording of metastases data in the Flatiron data set is considered unreliable (as shown by the large prevalence of patients without metastases) and therefore, IPTW adjustments on this variable were not considered a priority to avoid introducing systematic bias to the analysis
- The pembrolizumab monotherapy in UK clinical practice represents a PD-L1 (tumor proportion score) ≥50% patient population as per the EMA license.
    - The Flatiron dataset is a real world US based dataset. PD-L1 status is not recorded in the Flatiron dataset. However, the FDA license is PD-L1 (tumor proportion score) ≥1%, therefore, it is likely that majority of patients in the Flatiron database would have PD-L1 status of ≥1%. In the naïve comparison (Section B.2.9.4, Appendix L), pralsetinib was slightly more effective compared to pembrolizumab monotherapy in the PD-L1≥1% population compared to pembrolizumab monotherapy in the PD-L1≥50% (OS hazard ratio [redacted] vs [redacted]; PFS hazard ratio [redacted] vs [redacted]). However, these have not been adjusted for patient characteristics.
    - The pralsetinib population was included regardless of PD-L1 status. PD-L1 status was not reliably recorded in the ARROW clinical trial. However, as

pralsetinib is a *RET* inhibitor, there is not an established relationship between PD-L1 status and clinical outcomes. Therefore, using an ITT population for pralsetinib is not thought to have any bias on results

- The Flatiron database is a real-world evidence data base and therefore, it is possible that some bias may occur in the comparison between real world evidence studies and clinical trials. However, all efforts were undertaken in the design of the study and in the IPTW analysis in order to mitigate this bias
    - There was some remaining imbalance in age, smoking history and race after re-weighting in the pembrolizumab monotherapy comparison. Since smoking history is the most imbalanced factor thought to be a key driver of the results, and negatively affect the performance of pembrolizumab monotherapy, it is likely that the comparative analysis results in favour of pralsetinib hold true despite that. Indeed, had the balancing of characteristics worked perfectly, patients without smoking history in the pembrolizumab monotherapy arm (currently at 51% vs. 61%) would have been up-weighted even more driving the KM curves further down.

B.2.9.6 Summary of indirect treatment comparison results used in the base case

Indirect treatment comparison approaches with individual patient level data in the comparator arm are preferred so that the WT population can be adjusted to reflect the baseline characteristics of the *RET* fusion-positive population to ensure the indirect treatment comparison represents a *RET* vs (adjusted) *RET* comparison so that the patient population is aligned to the scope of this submission. For docetaxel monotherapy only, this was feasible to do using a Roche sponsored trial where individual patient data was available. For pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy, individual patient data was available from the Flatiron Health dataset. For docetaxel + nintedanib and pemetrexed + carboplatin, no individual patient data was available and therefore naïve comparisons were used.

Table 24 displays a summary of the hazard ratios from the indirect treatment comparison and the sources to inform the comparison for each comparator. Pralsetinib demonstrated statistically significant benefit in the untreated setting in OS, PFS and TTD against all comparators. A statistically significant survival benefit was also observed in the pre-treated setting.

Table 24: Summary of hazard ratios vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR (95% CIs)	PFS HR (95% CIs)	TTD HR (95% CIs)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	OAK trial (propensity score weighting ATT) (72, 77)
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	LUME-Lung 1 (naïve comparison); PFS assumed equal to docetaxel monotherapy(57)
Pemetrexed + carboplatin	[redacted]	[redacted]	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison)(78)

Note: For docetaxel monotherapy and docetaxel + nintedanib TTD where TTD was not available, PFS was used as a proxy. To avoid clinical implausibility, docetaxel + nintedanib was assumed to have equal PFS and TTD to docetaxel monotherapy
Where hazard ratio <1 favours pralsetinib
ATT, average treatment-effect on treated; EDM, enhanced data mart; HR, hazard ratio, PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

B.2.9.7 Uncertainties in the indirect treatment comparisons

- As this is a new therapeutic area, there is currently a paucity of literature on the prognostic value of *RET* fusion status, so it was assumed that *RET* fusion status is not independently prognostic for clinical outcomes in advanced NSCLC, and that after adjustment for differences in population characteristics, the treatment comparison is robust and unbiased to inform decision making. There is uncertainty about this in the literature
- When naïve comparisons were used for docetaxel + nintedanib and pemetrexed + carboplatin in pre-treated patients, some of the treatment effects in favour of pralsetinib may be attributed to bias owing to key cross-population differences. However, as shown with docetaxel monotherapy, the naïve and adjusted analyses yielded qualitatively very similar results for PFS and OS.
- Where Flatiron Health data EDM was used for pembrolizumab monotherapy in untreated patients, it was not possible to balance all key characteristics for the pembrolizumab monotherapy comparison, likely due to the large differences (i.e., limited overlap) in the baseline distributions. As smoking history, a key driver in pembrolizumab monotherapy effectiveness, remained imbalanced in favour of the comparator arm, it is plausible to assume that the residual bias is mitigated

    - In the main analyses all metastases-related variables were excluded from the confounder set for adjustment due to concerns of under reporting and the introduction of systematic bias
- As with any propensity score weighting analysis, it is impossible to rule out the influence of unobservable confounders. This potential bias, however, should be minimised by the balancing of observable patient characteristics across treatment groups (82-84)

The upcoming Phase III trial for pralsetinib in untreated *RET* fusion + population will address these issues (85).

B.2.10 Adverse reactions

Safety results were reported at data cut-off (06 November 2020) for the overall safety population with all tumour types treated at 400 mg QD of pralsetinib (n=528) and for the safety population of patients with NSCLC treated at 400 mg QD (n=281) (86). A summary of AEs is provided below.

All Phase 1 patients who were exposed to at least one dose of 400 mg QD pralsetinib were included in the safety population together with patients in Phase 2 for safety analyses.

Please note that the current safety data presented are subject to regulatory changes and further safety analyses may come available during the EMA filing process. Roche Products Ltd will share any additional data with NICE as and when it becomes available.

Table 25: Summary of AEs (overall safety population and patients with NSCLC treated at 400 mg QD)

Parameter, n (%)	Overall (All tumour types) n=528	*RET* fusion-positive NSCLC n=281
Any AE	525 (99.4)	279 (99.3)
≥Grade 3	406 (76.9)	212 (75.4)
TRAEs	493 (93.4)	264 (94.0)
≥Grade 3	291 (55.1)	155 (55.2)
SAE	288 (54.5)	166 (59.1)
Related SAEs	108 (20.5)	69 (24.6)
Deaths due to AEs	66 (12.5)	35 (12.5)
Deaths related to pralsetinib	6 (1.1)	2 (<1)

AE, adverse event; MedDRA, Medical Directory for Regulatory Activities; N, number of patients; NSCLC, non-small cell lung cancer; QD, once daily; SAE, serious adverse event; TRAE, treatment-related adverse event.

Pralsetinib was found to be well tolerated with a predictable and manageable safety profile in the overall safety population and in patients with *RET* fusion–positive NSCLC treated with

400 mg QD. A dose of 400mg in a QD schedule was appropriate for the *RET* fusion–positive NSCLC patient population. No risks were identified that were not expected with a protein kinase inhibitor being used as an antineoplastic agent in this patient population.

In the overall safety population, the most common AEs (reported in >25% of patients) were aspartate aminotransferase (AST) increased (46.0%), followed by anaemia (45.6%), constipation (41.9%), alanine aminotransferase (ALT) increased (33.9%), hypertension (32.6%), diarrhoea (29.4%), white blood cell (WBC) count decreased (26.9%), and pyrexia (25.2%). Overall, 93.4% of patients had treatment-related adverse events (TRAEs), and these were mainly increased AST (39.0%), anaemia (33.9%), increased ALT (28.8%), constipation (26.9%), neutrophil count decreased (22.7%), hypertension and WBC count decreased (25.2% each).

The most common related serious adverse events (SAEs) in the overall safety population were pneumonia (9.8%), disease progression (7.8%) and pneumonitis (4.5%). Pneumonia and pneumonitis are commonly seen in lung cancer patients.

AEs that were the primary or contributing reasons for permanent treatment discontinuation (including progressive disease and AEs that represented symptoms of disease progression) were reported in 14.4% of the overall safety population and 16.0% of the patients with *RET* fusion–positive NSCLC treated at 400 mg QD. The most common AEs leading to permanent treatment discontinuation excluding progressive disease were pneumonitis (1.9%) and pneumonia (1.7%).

The most common AEs leading to dose reduction (reported in >4% of patients) in the overall safety population were anaemia (7.8%), neutropenia (7.8%), neutrophil count decreased (7.5%), pneumonitis (6.4%), blood creatinine phosphokinase (CPK) increased (4.3%) and hypertension (4.3%). These were similar in the overall safety population and in patients with *RET* fusion–positive NSCLC treated at 400 mg QD.

Based on the results of ECG analyses, pralsetinib was not found to cause QT prolongation and there was no evidence of cardiac repolarisation prolongation in *RET* fusion–positive NSCLC patients.

B.2.10.1 Exposure to pralsetinib

Median (range) treatment duration in the safety population from ARROW was 9.46 (0.1, 33.9) months for the safety population, and 7.9 (0.3, 28.4) months for patients with *RET* fusion–positive NSCLC treated at 400 mg QD. The median dose intensity was 92.1% for patients with *RET* fusion–positive NSCLC.

Table 26: Summary of exposure to pralsetinib (overall safety population and patients with *RET* fusion–positive NSCLC treated at 400 mg QD)

	Overall (All tumour types) n=528	*RET* fusion-positive NSCLC n=281
Exposure, months[a]		
Median (min, max)	9.46 (0.1, 33.9)	7.89 (0.3, 28.4)
Relative dose intensity, %[b]		
Median (min, max)	91.1 (21, 100)	92.1 (27, 100)

Max, maximum; min, minimum; NSCLC, non-small cell lung cancer; QD, once daily.

[a]Defined as (treatment end date – treatment start date +1/30.4375.

[b]Defined as dose intensity/planned dose intensity x 100. Planned dose intensity is based on initial assigned daily dose.

B.2.10.2 Safety outcomes

In the overall safety population, 525 patients (99.4%) experienced any AEs, 493 (93.4%) experienced TRAEs, 291 (55.1%) experienced Grade ≥ 3 related AEs, 288 (54.5%) experienced SAEs, and 108 (20.5%) experienced treatment related SAEs. AEs in the overall safety population are summarised in Table 27.

Safety population was also evaluated in the 281 patients with *RET* fusion–positive NSCLC who initiated pralsetinib at 400 mg QD, of whom 19.6% discontinued treatment, with progressive disease as the primary reason for treatment discontinuation (3.6%). The most common AEs leading to treatment discontinuation were disease progression (2.8%), pneumonitis (1.9%), and pneumonia (1.7%).

In general, the safety profile in patients with *RET* fusion–positive NSCLC treated at 400 mg QD was similar to that of the overall safety population.

Common AEs

The most common AEs (reported in >25% of patients) in the overall safety population were AST increased (46.0%), anaemia (45.6%), constipation (41.9%), hypertension (32.6%), ALT increased (33.9%), diarrhoea (29.4%), WBC count decreased (26.9%), and pyrexia (25.2%; Table 25). There were no clinically meaningful differences between patients with *RET* fusion–positive NSCLC (n=281) and all patients (n=528) in the safety population treated at 400 mg QD.

In patients with *RET* fusion–positive NSCLC treated at 400 mg QD; the most common AEs were similar to those in the overall safety population.

Table 27: AEs with ≥10% incidence (overall safety population and patients with *RET* fusion–positive NSCLC both treated at 400 mg QD)

Preferred term, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Patients with any AE	525 (99.4)	279 (99.3)
Anaemia	241 (45.6)	129 (45.9)
AST increased	243 (46.0)	126 (44.8)
Constipation	221 (41.9)	118 (42.0)
Hypertension	172 (32.6)	96 (34.2)
ALT Increased	179 (33.9)	92 (32.7)
Neutrophil count decreased	128 (24.2)	81 (28.8)
Pyrexia	133 (25.2)	72 (25.6)
White blood cell count decreased	142 (26.9)	72 (25.6)
Diarrhoea	155 (29.4)	70 (24.9)
Fatigue	132 (25.0)	67 (23.8)
Cough	114 (21.6)	65 (23.1)
Blood creatinine increased	118 (22.3)	62 (22.1)
Neutropenia	116 (22.0)	61 (21.7)
Blood creatinine phosphokinase increased	86 (16.3)	53 (18.9)
Dry Mouth	84 (15.9)	47 (16.7)
Dyspnoea	89 (16.9)	47 (16.7)
Pneumonia	75 (14.2)	44 (15.7)
Dysgeusia	81 (15.3)	42 (14.9)
Oedema peripheral	82 (15.5)	42 (14.9)
Nausea	84 (15.9)	42 (14.9)
Asthenia	73 (13.8)	39 (13.9)
Back pain	60 (11.4)	38 (13.5)
Dizziness	70 (13.3)	38 (13.5)
Decreased appetite	80 (15.2)	38 (13.5)
Urinary tract infection	67 (12.7)	38 (13.5)
Hypokalaemia	69 (13.1)	38 (13.5)
Hypoalbuminemia	61 (11.6)	37 (13.2)
Hypophosphaetemia	55 (10.4)	35 (12.5)
Blood alkaline phosphate increased	55 (10.4)	35 (12.5)
Hypocalcaemia	109 (20.6)	34 (12.1)
Headache	82 (15.5)	34 (12.1)
Platelet count decreased	58 (11.0)	33 (11.7)
Hyperphosphataemia	94 (17.8)	32 (11.4)

Pneumonitis	55 (10.4)	32 (11.4)
Vomiting	65 (12.3)	32 (11.4)
Hyponatraemia	30 (10.7)	30 (10.7)
Leukopenia	49 (9.3)	30 (10.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; QD, once daily.

AEs were coded using MedDRA 19.1. If a patient had multiple occurrences of an AE, the patient was presented only once in the respective patient count. The events are reported in decreasing frequency as per the overall safety population.

Grade ≥3 AEs

AEs of Grade ≥3 were reported by 406 patients (76.9%) in the overall safety population and by 212 patients (75.4%) with *RET* fusion–positive NSCLC treated at 400 mg QD. The most common AEs of Grade ≥3 (reported in ≥10% patients) in the overall safety population were anaemia (17.2%), hypertension (16.1%), neutropenia (11.2%) and neutrophil count decreased (9.7%); these were also the most common AEs of Grade ≥3 for patients with *RET* fusion–positive NSCLC treated at 400 mg QD.

Table 28: AEs of Grade ≥3 with ≥10% incidence (overall safety population and patients with *RET* fusion–positive NSCLC both treated at 400 mg QD)

Preferred term, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Patients with any Grade ≥3 AE	406 (76.9)	212 (75.4)
Anaemia	91 (17.2)	46 (16.4)
Hypertension	85 (16.1)	45 (16.0)
Neutropenia	59 (11.2)	30 (10.7)
Neutrophil count decreased	51 (9.7)	36 (12.8)

AE, adverse event, MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; QD, once daily.

AEs were coded using MedDRA 19.1. If a patient had multiple occurrences of an AE, the patient was presented only once in the respective patient count. AEs are reported in a decreasing frequency as per the overall safety population.

Treatment-related AEs

In the overall safety population, 493 patients (93.4%) experienced ≥1 treatment-related AEs (TRAEs) and 108 (20.5%) experienced treatment relates SAEs. The most common TRAEs were AST increased (39.0%), anaemia (33.9%), ALT increased (28.8%), neutrophil count decreased (22.7%), constipation (26.9%), hypertension and WBC count decreased (25.2% each). All other TRAEs occurred in <25% of patients.

For patients with *RET* fusion–positive NSCLC treated at 400 mg QD, 264 (94.0%) experienced ≥1 TRAE and 166 (59.1%) experienced treatment related SAEs [125]. The most

common TRAEs were AST increased (40.6%), anaemia (35.9), ALT increased (29.6%), neutrophil count decreased (28.1%), constipation (26.0%), hypertension and WBC count decreased (24.9% each) and neutropenia (20.6%). All other TRAEs occurred in <20% of patients in this population.

Table 29: TRAEs with ≥10% incidence (overall safety population and patients with NSCLC treated at 400 mg QD)

Preferred term, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Patients with Any TRAE	493 (93.4)	264 (94.0)
AST increased	206 (39.0)	114 (40.6)
Anaemia	179 (33.9)	101 (35.9)
ALT increased	152 (28.8)	84 (29.6)
Neutrophil count decreased	120 (22.7)	79 (28.1)
Constipation	142 (26.9)	73 (26.0)
Hypertension	133 (25.2)	70 (24.9)
WBC count decreased	133 (25.2)	70 (24.9)
Neutropenia	109 (20.6)	58 (20.6)
Blood creatinine phosphokinase increased	81 (15.3)	49 (17.4)
Fatigue	58 (12.3)	42 (14.9)
Blood creatinine increased	76 (14.4)	41 (14.6)
Diarrhoea	79 (15.0)	39 (13.9)
Dysgeusia	69 (13.1)	37 (13.2)
Dry Mouth	63 (11.9)	35 (12.5)
Asthenia	53 (10.0)	30 (10.7)
Hyperphosphataemia	86 (16.6)	30 (10.7)
Pneumonitis	50 (9.5)	30 (10.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; QD, once daily; WBC, white blood cell.

Note: AEs were coded using MedDRA 19.1. If a patient had multiple occurrences of an AE, the patient was presented only once in the respective patient count. The events are presented in a decreasing frequency as per the overall safety population.

SAEs

SAEs were reported for 288 patients (54.5%) in the overall safety population, of whom 108 (20.5%) had treatment related SAEs. The most common SAEs in the overall safety population (occurring in ≥2% patients) were pneumonia (9.8%), disease progression (7.8%), pneumonitis (4.5%), anaemia (3.8%), sepsis (2.8%) and pyrexia (2.3%), most of which were also the most common SAEs in patients with *RET* fusion–positive NSCLC treated at 400 mg

QD. In patients with *RET* fusion–positive NSCLC treated at 400 mg QD, SAEs were reported for 166 (59.1%) patients.

The most common treatment related SAEs (occurring in ≥2 patients in the overall safety population) were pneumonitis (4.0%), pneumonia (2.7%), anaemia (1.9%), neutropenia (1.3%), sepsis and hypertension (<1% each).

Table 30: Pralsetinib SAEs occurring in ≥2% patients (overall safety population and patients with NSCLC treated at 400 mg QD)

Preferred term, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Patients with SAEs	288 (54.5)	166 (59.1)
Pneumonia	52 (9.8)	33 (11.7)
Disease progression	41 (7.8)	21 (7.5)
Pneumonitis	24 (4.5)	13 (4.6)
Anaemia	20 (3.8)	9 (3.2)
Sepsis	15 (2.8)	8 (2.8)
Pyrexia	12 (2.3)	8 (2.8)
Dyspnoea	10 (1.9)	6 (2.1)
Urinary tract infection	18 (3.4)	6 (2.1)
Pleural effusion	10 (1.9)	6 (2.1)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; QD, once daily; SAE, serious adverse event.

Note: AEs were coded using MedDRA 19.1. If a patient had multiple occurrences of an AE, the patient was presented only once in the respective patient count. The related SAEs are reported in a decreasing frequency as per the overall safety population.

AEs leading to dose modification

AEs leading to dose modifications were reported for 395 patients (74.8%) in the overall safety population. In both populations, most of the dose modifications were dose interruptions (approximately 68%), and the rest were dose reductions (45%).

The most common reasons for dose interruption were similar for the overall safety population and patients with *RET* fusion–positive NSCLC treated at 400 mg QD. In the safety population, these were anaemia (8.1%), neutropenia (8.0%), neutrophil count decreased (6.4%), pneumonitis (5.1%), blood CPK increased and hypertension (4.0% each), WBC count decreased (3.4%), fatigue (3.0%), lymphocyte count decreased (3.0%) and lymphopenia (2.3%).

The most common events leading to dose reduction (reported in >2% of patients) were similar in the overall safety population and for patients with *RET* fusion–positive NSCLC treated at 400 mg QD. In the overall population, the most common AEs leading to dose

reductions were, anaemia (8.1%), neutropenia (8.0%), neutrophil count decreased (6.4%), pneumonitis (5.1%), blood CPK increased and hypertension (4% each), WBC count decreased (3.4%), fatigue (3.0%), lymphocyte count decreased (3.0%) and lymphopenia (2.3%).

AEs leading to treatment discontinuation were reported in 14.4% of patients in the overall safety population and 16.0% in *RET* fusion–positive NSCLC patients treated at 400 mg QD. The most common AEs (occurring in >1% of patients) leading to treatment discontinuation were disease progression (2.8%), pneumonitis (1.9%), and pneumonia (1.7%).

Table 31: Summary of dose modifications (overall safety population and patients with NSCLC treated at 400 mg QD)

Type of dose modification, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Dose escalation	514 (97.3)	276 (98.2)
Dose interruption	372 (70.5)	196 (69.8)
Due to AE	352 (66.7)	185 (65.8)
Dose reduction	244 (46.2)	125 (44.5)
Due to AE	236 (44.7)	123 (43.8)
Dose discontinuation	241 (45.6)	130 (46.3)
Due to AE	74 (14.0)	44 (15.7)
Due to related AE	34 (6.4)	22 (7.8)
Dose missing	142 (26.9)	65 (23.1)
Due to AE	4 (<1)	2 (<1)

AE, adverse event; NSCLC, non-small cell lung cancer; QD, once daily.

Table 32: AEs leading to permanent treatment discontinuation in ≥2 patients (overall safety population and patients with NSCLC treated at 400 mg QD)

Preferred term, n (%)	Overall (All tumour types) n=528	*RET* fusion–positive NSCLC n=281
Patients with any AE[a]	91 (17.2)	55 (19.6)
Disease progression	15 (2.8)	10 (3.6)
Pneumonitis	10 (1.9)	7 (2.5)
Pneumonia	9 (1.7)	7 (2.5)
Sepsis	4 (<1)	3 (1.1)
Death	3 (<1)	2 (<1)
Dyspnoea	2 (<1)	2 (<1)
Thrombocytopenia	2 (<1)	2 (<1)
Fatigue	2 (<1)	1 (<1)
Hyponatraemia	2 (<1)	1 (<1)

Neutropenia	2 (<1)	1 (<1)
Pulmonary embolism	2 (<1)	1 (<1)
Respiratory failure	2 (<1)	1 (<1)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; QD, once daily.

[a]Based on disposition data, there is a different number of patients with AEs leading to treatment discontinuation. This is because disposition data only summarise the primary reason for treatment discontinuation, while the AE dataset reflects patients with AEs as either the primary or a contributing reason for treatment discontinuation. These would include cases where the primary reason for discontinuation was clinical progression (symptomatic deterioration) where the AE dataset captures symptoms of clinical progression as AEs with the action "treatment discontinuation".

Deaths

Sixty-six patients (12.5%) died during the study due to AEs, including 35 patients with *RET* fusion–positive NSCLC (12.5%). Six patients (1.1%) died due to TRAEs (investigator assessed): rhabdomyolysis, pneumonia, Pneumocystis jirovecii pneumonia, pneumonitis and death [2 patients, unknown cause of death in 1 patient and multifactorial cause in 1 patient]. Treatment related fatal events due to rhabdomyolysis and pneumonia were reported between 22 May 2020 and 06 November 2020.

B.2.11 Ongoing studies

The ARROW study is currently ongoing. Timelines for the final analysis are to be confirmed as this will be event driven, but is expected to be available by [redacted].

Additionally, the Phase 3 AcceleRET Lung was initiated in June 2020, which is a multicentre trial that will evaluate pralsetinib at 400 mg QD against SOC platinum-based chemotherapy in patients with *RET* fusion–positive NSCLC (85).

B.2.12 Innovation

Currently, there is a lack of available targeted therapies for patients with *RET* fusion-positive NSCLC; therefore, unnecessary healthcare resource use and patients' time are wasted in achieving sub-optimal efficacy outcomes with immunotherapy and/or IV chemotherapy, combined with higher rates of difficult to treat adverse events. A more effective, precision-based treatment model identifies specific molecular alterations, or biomarkers that drive malignant transformation in patients, allowing for the selection of individualised treatments tailored to each unique cancer case. This new approach is provided by pralsetinib and offers an effective targeted and labelled treatment option for all adult patients with *RET* fusion–positive NSCLC. This is of particular importance to untreated patients with *RET* fusion–positive NSCLC given the unmet need among this patient population and the benefits

obtained from earlier targeted therapy, together with the avoidance of unnecessary toxicity from systemic treatments.

Testing for *RET* fusion-positive NSCLC and treating appropriately diagnosed patients with pralsetinib is a more cost-effective approach compared with the one-size-fits-all option currently available using non-targeted chemotherapy. The shift from the traditional one-size-fits-all treatment model to personalised healthcare has the potential for better clinical responses, improved QoL and overall patient care. This can avoid unnecessary healthcare resource use while freeing up patients' time.

Pralsetinib is administered as a once-daily oral dose by the patients themselves, or their caregivers, at home or in an ambulatory setting (1). Oral administration alleviates the burden associated with the traditional use of non-targeted IV chemotherapy. For instance, patient preference for oral therapy is largely associated with the reduced need for hospital admissions due to lengthy treatment schedules with IV chemotherapy and the reduced frequency of clinical visits (87), which is critical given that clinical experts confirmed to Roche that chemotherapy units in UK clinical practice are in crisis due to severe capacity constraints (3). Additional benefits of oral therapy, versus IV treatment, include alleviation of healthcare resource use and the requirement for hospital beds (61, 88). Oral therapy can also eliminate the risk of infusion-related adverse reactions that are common with cancer treatment (89).

Oral administration also provides patients with the freedom to remain active, take ownership of their own disease management and remain fully engaged members of society for longer. The patient and caregiver burden are also reduced, as pralsetinib reduces the need for hospital travel time and costs, while the use of pralsetinib may reduce the productivity losses otherwise associated with patients that have *RET* fusion-positive NSCLC on IV chemotherapy due to reductions in the amount and duration of sickness leave due to treatment infusions.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The era of precision medicine has resulted in the identification of a number of genomic alterations that can be targeted with novel therapies. *RET* gene fusions are present in approximately 1% to 2% of NSCLC and they are emerging as a new targetable driver for this rare population of NSCLC. Patients with *RET* fusions tend to be younger (<60 years of age), non-smokers with lung adenocarcinomas, and patients presenting these alterations are more likely to be in an advanced stage with multiple metastatic lesions/sites, including CNS metastases

Overall, there is accumulating evidence that the currently recommended treatment options for patients with advanced NSCLC and documented *RET* fusions do not offer the efficacy that has been achieved in patients with NSCLC and other identified oncogenes (such as EGFR and ALK). Existing non-targeted therapy for these patients is associated with significant toxicity and safety risks. To date, no selective *RET*-directed targeted therapies have received NICE approval for the treatment of molecularly defined populations of patients with *RET*-mutant or *RET* fusion–positive solid tumours. Therefore, *RET* fusion–positive NSCLC remains an unmet need that requires new therapeutic options to improve outcomes and generate cost savings, especially in untreated patients given the benefits associated with earlier targeted therapy and the risk of unnecessary potential toxicity associated with standard systemic, non-targeted treatments.

Pralsetinib is a specific and highly potent inhibitor of the *RET* tyrosine kinase. The targeted mechanism of action of pralsetinib provides strong antitumor activity and durable response in patients with *RET* fusion-positive NSCLC, as is the case with targeted therapies for other mutations such as crizotinib for ALK and ROS1-rearranged NSCLC. In addition, as an oral treatment pralsetinib also provides a more flexible and convenient option, and alleviates the economic burden, stress and discomfort associated to IV treatments.

The safety, tolerability, PK, pharmacodynamics, and antineoplastic activity of pralsetinib in patients with advanced, unresectable, *RET*-altered NSCLC, MTC, and other *RET*-altered solid tumours was evaluated in the Phase 1/2, open-label, ARROW study. A conventional RCT for a rare genomic alteration such as *RET* fusion-positive NSCLC was not chosen to ensure timely patient access to the treatment, given the rarity of *RET* rearrangements. The successful tumour-agnostic approvals of innovative anti-tumour agents like entrectinib and pembrolizumab have also demonstrated the growing importance of ‘basket’ trials like ARROW in oncology drug development. The experience with other biomarker-targeted therapies for NSCLC have generated evidence that outstanding ORRs observed in uncontrolled trials when accompanied by evidence of a long DOR may likely translate to long-term efficacy on OS and PFS in the context of subsequent randomised controlled trials. By focusing on specific molecular features regardless of tumour type, basket trials can encompass much less common cancer subtypes that are often underrepresented in conventional clinical trials. For all those reasons, the use of a single-arm trial for pralsetinib’s assessment was considered appropriate. Further evidence will be generated via ongoing clinical trials (AcceleRET).

Patients were eligible for enrolment into ARROW regardless of whether they had received prior or treatment or not, therefore this trial provides evidence to support the anticipated line

agnostic indication. UK clinical experts confirmed to Roche that the baseline characteristics of patients enrolled in ARROW are similar to other oncogene driver trials and broadly reflect UK clinical practice (3).

Eligibility for ARROW was determined by local assessment of *RET* fusion status through various testing methods, including NGS or FISH. Suitable tests to identify *RET* fusion-positive people are included in the 2020/2021 National Genomic Test Directory (7), therefore, the identification of eligible patients for pralsetinib is not considered to result in added costs or an additional resource burden. However, clinical expert advice obtained by Roche confirmed that testing for *RET* fusions is not routinely carried out, and there is considerable variation in the approaches taken to testing and turnaround times to obtaining results. Clinical experts emphasised the importance of implementing molecular screening strategies for the detection of *RET* rearrangements in patients with advanced NSCLC and other solid tumours, which is supported by the promising activity of pralsetinib in the ARROW study. Clinical experts added that they hope to see improvements in the implementation of testing by the end of 2021, with the siginifcant number of possible molecular targets (and associated treatments) for NSCLC providing rationale to screen for multiple targets via NGS panels.

The results of the ARROW study show that pralsetinib was well tolerated and displayed clinical activity in patients with *RET* fusion-positive NSCLC, including intracranial responses, regardless of previous therapy, with response rates of 62% in patients who had received previous platinum chemotherapy and 79% in treatment-naive patients who were not candidates for standard therapies.

In the ARROW study, pralsetinib showed rapid and durable clinical activity in patients with advanced *RET* fusion-positive NSCLC. In patients who received prior systemic treatment, median duration of response was 22.3 months, attesting to the durability of response, while median PFS was [redacted] months. Along with the response rate of 64%, these data are favourable when considered in the context of historical outcomes seen with second-line chemotherapy regimens (relevant comparators to the current submission) in patients without targetable molecular drivers, where overall response rates range from 3.3% to 9.1%, median progression-free survival does not exceed 3.4 months and median OS ranges from 7.9 to 10.9 months (56, 57).

Pralsetinib also showed favourable activity in the untreated patient population. This patient group presented with several unfavourable prognostic factors at baseline, for example, 46% were current or former smokers, with 32% having brain metastases, a somewhat higher incidence than might be expected in an untreated, metastatic population (37). Tumour

shrinkage was observed in all evaluable untreated patients. The response rate (79%) observed with pralsetinib in this population is similar to rates seen with other targeted therapies in oncogene-driven lung cancers, including osimertinib in EGFR-mutant NSCLC (80%), alectinib in ALK-positive NSCLC (83%), and entrectinib (77%) and crizotinib (72%) in ROS1 fusion-positive NSCLC (90-93).

The data for pralsetinib in untreated patients further validates *RET* as a therapeutic target and solidifies the overall targeted therapy paradigm in oncogene-driven NSCLC. Moreover, given the modest activity of checkpoint inhibitors in unselected patient populations, and specifically in patients with *RET* fusion-positive NSCLC, the findings from ARROW support a role for first-line selective *RET* inhibition with pralsetinib within this NSCLC treatment paradigm.

The development of CNS metastases is common and a poor prognostic factor in patients with *RET* fusion-positive NSCLC (36). Preclinical studies of pralsetinib have shown blood–brain barrier penetration and activity against intracranial tumours (63). Pralsetinib showed intracranial activity in patients with *RET* fusion-positive NSCLC and measurable baseline brain metastases in the ARROW study, including the inducement of intracranial complete responses.

Overall, pralsetinib was well tolerated at a dose of 400 mg once daily in patients with *RET* fusion-positive NSCLC. Adverse events leading to pralsetinib discontinuation were uncommon, occurring in 16% of *RET* fusion-positive NSCLC patients. Although it is difficult to make cross-trial comparisons between different study populations, the overall frequency of adverse events with pralsetinib was generally similar to another *RET* inhibitor, selpercatinib, although with a slightly different profile. Grade 3 or worse QT interval prolongation was reported in 4% of patients in the LIBRETTO-001 study and is a safety warning for selpercatinib (94), although these events were not observed with pralsetinib in ARROW.

As ARROW was a single arm study, it provided no estimate of relative treatment effectiveness. To inform the current appraisal, it is necessary to estimate treatment effectiveness against the untreated and pre-treated comparators outlined in Section B.1.1. Therefore an indirect treatment comparison was conducted (Section B.2.9). There is a paucity of evidence available for *RET* fusion-positive patient populations in both the published literature and real world evidece. Therefore, in order to inform the indirect treatment comparison WT populations were considered. To account for differences in characteristics, patients in the comparator arm were adjusted to reflect a *RET* fusion-positive population (as per ARROW) where possible.

Table 33 displays a summary of the hazard ratios from the indirect treatment comparison and the sources to inform the comparison for each comparator. Pralsetinib demonstrated statistically significant benefit in the untreated setting in OS, PFS and TTD against all comparators. A statistically significant survival benefit was also observed in the pre-treated setting. A summary of the uncertainties in the indirect treatment comparison is provided in Section B.2.9.7.

Table 33: Summary of hazard ratios vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR (95% CIs)	PFS HR (95% CIs)	TTD HR (95% CIs)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	OAK trial (propensity score weighting ATT) (72, 77)
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	LUME-Lung 1 (naïve comparison); PFS assumed equal to docetaxel monotherapy (57)
Pemetrexed + carboplatin	[redacted]	[redacted]	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison)(78)

Note: For docetaxel monotherapy and docetaxel + nintedanib TTD where TTD was not available, PFS was used as a proxy. To avoid clinical implausibility, docetaxel + nintedanib was assumed to have equal PFS and TTD to docetaxel monotherapy
Where hazard ratio <1 favours pralsetinib
ATT, average treatment-effect on treated; EDM, enhanced data mart; HR, hazard ratio, PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Conclusion

Pralsetinib is a highly selective and potent *RET* inhibitor and oral precision therapy designed to treat *RET*-altered cancers. Given the degree of unmet medical need and the potential benefits of earlier targeted treatment, together with the preference of UK clinical experts, the untreated population is the primary focus of the current appraisal, although evidence in the pre-treated setting is also provided in accordance with the anticipated indication.

Data from the ARROW study demonstrate that pralsetinib elicits clinically meaningful and durable responses in advanced *RET* fusion-positive NSCLC in both the untreated population and pre-treated patients, including those with CNS metastases. Moreover, pralsetinib is generally well tolerated, with a low discontinuation rate and manageable treatment-related AEs. Therefore, the availability of pralsetinib will provide a much needed targetted treatment option for all patients with *RET* fusion-positive NSCLC, especially untreated patients as

pralsetinib will spare this population from the poor outcomes and unnecessary potential toxicity associated with standard non-targeted therapies, whilst also freeing up capacity in the healthcare system.

Table 34: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real-world data from a Flatiron Health-Foundation Medicine Clinico-Genomic database and Guardant Health database of *RET* fusion-positive lung cancer patients demonstrated that median OS in response to first-line immunotherapy was 19.1 months (54). Mean OS in the economic model for untreated pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy is estimated to be [redacted] and [redacted] months respectively. Given these are from real world evidence and have been adjusted on patient characteristics to reflect a *RET* patient population, results are considered the most robust available. No published survival data for *RET* fusion positive NSCLC patients in the pre-treated setting are available, however median OS with second-line chemotherapy ranges in wild-type patients ranges from 7.9 to 10.9 months (56, 57). Mean OS in the economic model for pre-treated comparators is estimated to range from [redacted] months. Results align with clinical expert recommendations for life expectancy. Results from the economic model also align with the committee view in the selpercatinib appraisal ID3743 in the pre-treated indication where the short-life criterion was likely to be met. In summary, life expectancy for current standard of care in *RET* fusion-positive advanced NSCLC is expected to be less than 24 months in both the untreated and pre-treated setting.	B.1.3.2 (page 29)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional	Median PFS in the treatment-naïve and prior systemic treatment subgroups were [redacted] months and [redacted] months, respectively.	B.2.6.2 (pages 54-58)

3 months, compared with current NHS treatment	Estimated OS rates at 12 months for treatment-naïve and prior systemic treatment subgroups were [redacted] and [redacted] respectively. Mean OS in the economic model for untreated pralsetinib is estimated to be [redacted]months. Therefore, it's estimated that pralsetinib leads to an extension to life of [redacted]months and [redacted]months against untreated pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy respectively. Mean OS in the economic model for pre-treated pralsetinib is estimated to be [redacted] months. Therefore, it's estimated that pralsetinib leads to an extension to life of [redacted] months against pre-treated comparators. Clinical experts confirmed to Roche that treatment with pralsetinib would extend life by greater than 3 months (3)	

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify relevant cost-effectiveness studies from the published literature and from NICE technology appraisals as per NICE guidance. The SLR was carried out on 09 October 2020 to identify studies in *RET* fusion-positive NSCLC that included published economic evaluations.

A detailed description of the search strategy, extraction methods, as well as an overview of the identified studies are provided in Appendix G.

The electronic database searches identified a total of 2,397 citations. Following removal of 518 duplicates, 1,879 citations were screened on the basis of title and abstract. A total of two citations were considered to be potentially relevant for the economic evaluation SLR; however, both were excluded upon full text review. Hand searching yielded no additional relevant articles or previous HTA submissions for inclusion. Therefore, no published economic evaluations were identified for final inclusion in the economic evaluation SLR.

B.3.2 Economic analysis

B.3.2.1 Patient population

The patient population included in the economic evaluation consisted of adult patients with *RET* fusion-positive advanced NSCLC not previously treated with a *RET* inhibitor. This is in line with the proposed marketing authorisation and the final NICE scope. The proposed marketing authorisation is line-agnostic, meaning patients are eligible to be treated with pralsetinib in all lines of treatment as per the decision problem (Section B.1.1). The main body of clinical evidence for pralsetinib was derived from ARROW, which included both untreated and pre-treated *RET* fusion-positive NSCLC subjects, among other disease types.

The baseline characteristics of the patients included in the model are presented in Table 8.

Due to the unmet medical need in all *RET* fusion-positive patients in the UK, Roche's priority is that all *RET* fusion-positive advanced NSCLC patients have a *RET* inhibitor available as a treatment option. Roche notes the ongoing appraisal for selpercatinib in the pre-treated population. If selpercatinib were to attain entry to the CDF as is the stated aim in the appraisal, pre-treated patients would be served with a *RET* inhibitor. Consequently, an unmet need for untreated patients would remain. Further, clinical experts consulted by Roche expressed a desire to have a *RET* inhibitor available in the untreated due to the likely benefits of earlier targeted therapy for *RET* fusion-positive patients.

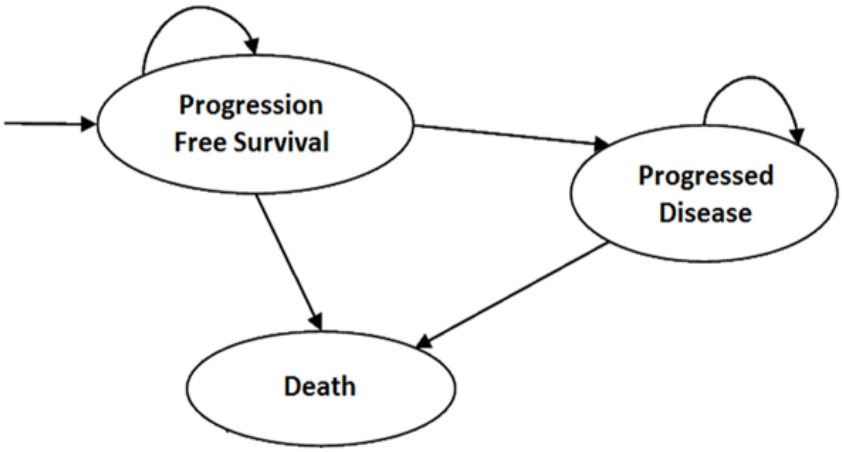
In order to align with the anticipated licence and the scope, Roche has submitted economic analyses in both untreated and pre-treated populations. However, based on the degree of unmet medical need and the potential benefits of earlier targeted treatment, the untreated population is the primary focus for pralsetinib in this appraisal. This position was validated by clinical experts in an advisory board and [redacted] who stated a preference for the usage of pralsetinib in the untreated population.

B.3.2.2 Model structure

A *de novo* economic model was developed using the partitioned survival model (PSM) approach to inform decision-making for pralsetinib in untreated *RET* fusion-positive NSCLC. An additional analysis was also provided in the corresponding pre-treated population. The model structure was identical across the untreated and pre-treated analyses. The *de-novo* economic model was developed in Microsoft Excel. The model is an area-under-the-curve PSM. This is consistent with the majority of economic models developed for recent NICE submissions in NSCLC (including ID3743) (71) and in line with Decision Support Unit (DSU) guidance (95). An important benefit of the PSM approach is that modelling of OS and PFS is based on study-observed events, which is expected to accurately reflect disease progression and the survival profile of patients treated with pralsetinib.

The model includes three mutually exclusive health states: “progression-free (PF)”, “progressed disease (PD)” and “death” as shown in Figure 31.

Figure 31: Economic model structure

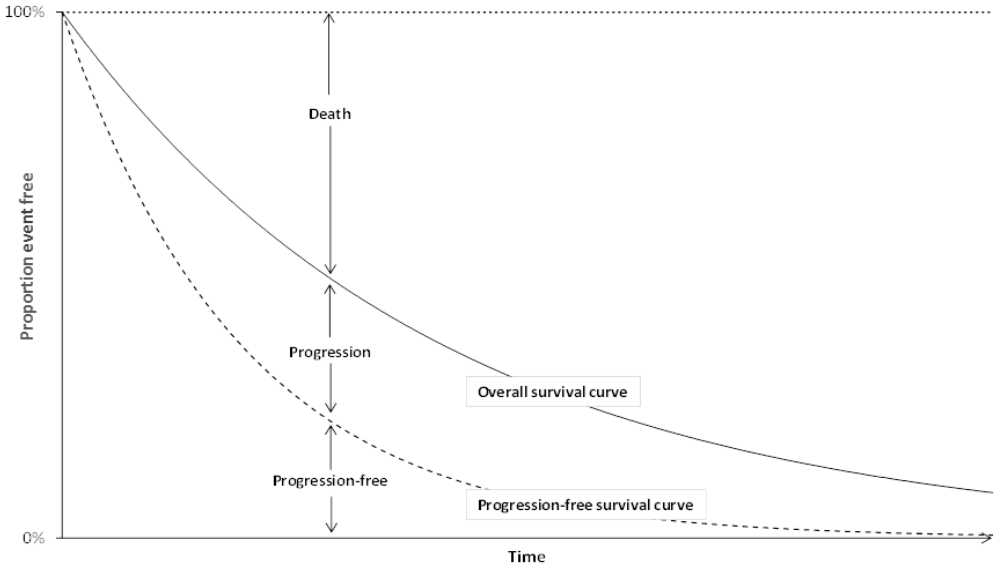


All patients enter the model in the PF health state and remain in this health state until they progress. Upon progression, patients either transition into the PD health state or enter the absorbing health state of death. Patients in the PD health state stay in that health state until death. Patients cannot transition to an improved health state (i.e. from PD to PF), a restriction that is consistent with previous economic modelling in oncology.

The proportion of patients in each health state at any time is defined by the partitioning of alive patients alive into “PF” and “PD” at discrete time points, based on the PFS and OS. The proportion of patients falling into the PF health state is represented by those patients in PFS. The proportion of patients falling into the PD health state is the difference between OS and PFS, as illustrated in Figure 32. PFS and OS in the pralsetinib untreated and pre-treated models are taken from the ARROW trial.

The definition of the PF health state used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the ARROW trial: PD was defined following the RECIST 1.1 criteria.

Figure 32: Example of a PSM



PSM, Partitioned survival model

PFS and OS for comparators are modelled by applying hazard ratios from the indirect treatment comparison to the pralsetinib arms as outlined in Section B.2.9. Hazard ratios from the indirect treatment comparison were estimated by comparing PFS and OS in the single-arm clinical trial ARROW to available sources for comparators. Table 35 displays a summary of the hazard ratios from the indirect treatment comparison and the sources to inform the comparison for each comparator. Given the paucity of evidence in *RET* fusion-positive patient populations, advanced NSCLC populations were used for comparators and adjustments were made to match to baseline characteristics in the ARROW population where possible. In the untreated population, the indirect treatment comparison used data from the Flatiron dataset adjusted for patient characteristics using IPTW.

Table 35: Summary of HRs vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR (95% CIs)	PFS HR (95% CIs)	TTD HR (95% CIs)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT) (79)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	OAK trial (propensity score weighting ATT; TTD assumed equal to PFS) (72, 77)
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	LUME-Lung 1 (naïve comparison; PFS and TTD assumed equal to docetaxel monotherapy) (57)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison; TTD assumed equal to PFS) (78)

Note: For docetaxel monotherapy and docetaxel + nintedanib TTD where TTD was not available, PFS was used as a proxy. To avoid clinical implausibility, docetaxel + nintedanib was assumed to have equal PFS and TTD to docetaxel monotherapy
Where hazard ratio <1 favours pralsetinib
CI, confidence interval; HR, hazard ratio, PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

For each health state, a specific cost (section B.3.5) and utility (section B.3.4.5) is assigned for each time period (represented by a model cycle). Treatment costs are modelled by time to treatment discontinuation (TTD) where available (95). Pralsetinib TTD is available from the ARROW trial. For comparators where TTD is unavailable, an equal treatment effect between pralsetinib vs. comparator PFS and TTD was assumed. Health state utility values were taken from the available published literature.

Costs and utilities are multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle. These are then added across all cycles in the model time horizon to find the total costs and QALYs which in turn are used to calculate incremental cost per life years gained (LYG) and the incremental cost per QALY gained. This appropriately reflects the decision problem.

A monthly model cycle was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death. Transition between health states can occur at any time within the cycle. In line with the NICE reference case, a half-cycle correction was applied to mitigate bias.

The economic model base-case uses a time horizon of 25 years, which was considered to be sufficiently long enough to reflect a lifetime perspective and capture all important differences in costs or outcomes between the technologies being compared. This takes into consideration:

1. Prognosis of patients treated in this setting
2. Expected survival times following present NHS treatment in this setting
3. The maximum plausible impact of improved outcomes following treatment with pralsetinib**.**

The time horizon is also consistent with the time horizon accepted by the ERG in the selpercatinib appraisal (ID3743) (71). Scenario analysis is provided considering both shorter and longer time horizons.

The population included in the economic evaluation is consistent with the population in the pivotal study (ARROW) and the anticipated licence. The untreated patient population is considered to be the focus patient population for pralsetinib in this appraisal. In order to align with the NICE final scope, an economic evaluation has also been conducted with the pre-treated population.

Table 36 details the main features of this economic analysis as compared with the selpercatinib appraisal.

Following the SLR, the selpercatinib submission (ID3743, including the company submission, ERG report and cost-effectiveness model) was made available to Roche on 20th May 2021 as part of the technical engagement process. This represented an economic evaluation in *RET* fusion-positive NSCLC to inform decision making for a NICE submission. Both selpercatinib and pralsetinib will look to establish a NSCLC *RET* fusion-positive treatment pathway. However, patients in the selpercatinib appraisal (ID3743) represent a pre-treated population whereas patients in the current appraisal represent all-lines. Given the similarities between the current appraisal and the selpercatinib appraisal, this was used to guide the development of the current economic evaluation with guidance taken from the ERG report to ensure the acceptability of the approach taken.

Table 36: Features of the economic analysis

	Previous appraisals	**Current appraisal**	
Factor	**ID3743**	**Chosen values**	**Justification**
Patient population	Pre-treated *RET* fusion-positive NSCLC patients	*RET* fusion-positive NSCLC patients	In line with anticipated marketing authorisation for pralsetinib. The patient population is split into untreated patients and pre-treated patients
Model structure	Partitioned survival model	Partitioned survival model	Model accurately reflects disease progression, trial endpoints and key aims of treatment for *RET* fusion-positive NSCLC patients. Partitioned survival modelling is a commonly used approach across oncology NICE appraisals

Time horizon	25 years	25 years	A lifetime horizon considered sufficient to capture all costs and QALYs associated with treatments
Cycle length	1-week	1-month	Deemed a sufficient length of time to account for changes in PFS, TTD and OS
Half-cycle correction	No	Yes	In line with the NICE reference case
Source of utilities	**Untreated** PF: 0.794 PD: 0.678 (TA654 preferred values by the committee) **Pre-treated** PF: 0.713 PD: 0.688 (TA713)	**Untreated** PF: 0.794 PD: 0.678 (TA654 preferred values by the committee) **Pre-treated** PF: 0.713 PD: 0.628 (TA713, preferred values by the committee as recommended by ERG in ID3743)	Utilities elicited directly from the ARROW trial were not suitable to inform the current economic model. Therefore, utilities were aligned with those recommended in selpercatinib appraisal (71) (Section B.3.4)
Source of costs	NHS reference costs, PSSRU, BNF, eMIT • Acquisition • Administration • Subsequent treatments • Monitoring • Health state • End of life • Adverse events	NHS reference costs, PSSRU, BNF, eMIT • Acquisition • Administration • Subsequent treatments • Health state • End of life • Adverse events	Costs and sources included commonly used in oncology NICE appraisals as per the NICE reference case. The costs associated with genomic testing have not been included in the base case analysis due to the imminent implementation of national genomic testing (48, 96) (Section B.3.5.5) but have been included as a scenario analysis.
Discount for utilities and costs	3.5%	3.5%	In line with the NICE reference case
Perspective	NHS/PSS	NHS/PSS	In line with the NICE reference case

BNF, British National Formulary; eMIT, electronic market information tool; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; PSSRU, Personal Social Services Research Unit; *RET*, rearranged during transfection; TTD, time-to-treatment discontinuation

B.3.2.3 Intervention technology and comparators

The final scope intervention is pralsetinib for the treatment of *RET* fusion-positive advanced NSCLC in all lines of treatment. Pralsetinib was included in the model as per the proposed licensed dosing regimen (administered orally at a dose of 400 mg QD until disease progression or unacceptable toxicity).

As outlined in Section B.1.1, the primary comparator in the untreated analysis will be pembrolizumab + pemetrexed + chemotherapy with a secondary analysis against

pembrolizumab monotherapy. The primary comparator for the pre-treated economic evaluation is docetaxel monotherapy with secondary analyses against docetaxel + nintedanib and an additional analysis provided against platinum-based chemotherapy +/- pemetrexed. The dosing and administration frequencies for comparators were applied in the model in line with their marketing authorisations and UK clinical practice:

- Untreated: Pembrolizumab + pemetrexed + chemotherapy:
    - Pembrolizumab administered intravenously (IV) 200 mg Q3W
    - Pemetrexed administered IV 500 mg/m^2 Q3W
    - Platinum-based chemotherapy (either or):
        - Cisplatin administered IV 75 mg/m^2 Q3W
        - Carboplatin administered 500 mg/m^2 Q3W
- Untreated: Pembrolizumab monotherapy
    - Pembrolizumab administered IV 200 mg Q3W
- Pre-treated: Docetaxel monotherapy
    - Docetaxel administered IV 75 mg/m^2 Q3W
- Pre-treated: Docetaxel + nintedanib
    - Docetaxel administered IV 75 mg/m^2 Q3W (day 1)
    - Nintedanib administered orally 200mg (twice daily on days 2-21)
- Pre-treated: platinum-based chemotherapy +/- pemetrexed
    - Pemetrexed administered IV 500 mg/m^2 Q3W
    - Platinum-based chemotherapy (either or):
        - Cisplatin administered IV 75 mg/m^2 Q3W
        - Carboplatin administered 500 mg/m^2 Q3W

B.3.3 Clinical parameters and variables

The primary source for clinical data for pralsetinib in the economic model is the ARROW study. ARROW is a phase I/II, global, single-arm, open-label, multicentre study in patients with *RET* fusion–positive NSCLC and other advanced solid tumours. Full study details are outlined in Section B.2.3. The *RET* fusion-positive NSCLC population of ARROW will inform the clinical evidence base for pralsetinib pertaining to this submission. The unrestricted efficacy population was used for analysis.

OS, PFS and TTD results from ARROW were extrapolated to the time-horizon of the model as lifetime results are not available for subjects in the ARROW study. The data cut used was the clinical cut-off date of 06 November 2020.

Guidance from the NICE DSU was followed to identify base-case parametric survival models for OS, PFS and TTD (95). All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Further details on the model validation are reported in section B.3.10. Clinical expert opinion was also utilised to validate the extrapolation approach taken.

As no comparators were included in ARROW, an indirect treatment comparison was conducted to estimate relative effectiveness. Survival estimates for untreated and pre-treated comparators in the model were generated by the indirect treatment comparison as described in section B.2.9. Survival from comparators were estimated by applying the hazard ratios from the indirect treatment comparison to the pralsetinib arm. Given an indirect treatment comparison was used, proportional hazard between pralsetinib and comparators was assumed. In curve selection, distributions which support the proportional hazards assumption were preferred.

The remainder of this section outlines the methods used for modelling OS, PFS and TTD in the economic model.

B.3.3.1 Untreated

B.3.3.1.1 OS extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib untreated OS data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 37 provides the AIC and BIC statistics for pralsetinib.

Table 37: Summary of goodness of fit for untreated OS – pralsetinib

	OS – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; OS, overall survival

Based on the AIC values for pralsetinib, the best fitting parametric model for OS is the exponential curve. However, given small differences between AIC and BIC values, all parametric models can be considered to show a similar fit. It should be noted that AIC and BIC tests are based only upon the relative fit of parametric models to the observed data. While these tests are useful to determine which models fit the observed data best, they cannot provide information on how suitable a parametric model is for the time period beyond the final trial follow-up. Therefore, the AIC and BIC tests address only the internal validity of fitted models, but not their external validity. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 33).

Figure 33: Parametric extrapolations to model untreated OS for pralsetinib

[redacted]

OS, overall survival

All curves provide a good visual fit to the observed data. However, given the immaturity of the data, a large proportion of OS across the model time horizon is measured by the extrapolated part of the curve. Given the importance of the extrapolated period to model survival (and therefore results) and the large disparity in long-term survival predictions from the different parametric curves, a key factor in curve selection was long-term clinically plausibility in the extrapolated period.

In order to inform long-term clinically plausibility of parametric models and to determine the OS curve selection used in the model base-case, an advisory board was held. Clinical experts were asked to predict plausible ranges for OS for pralsetinib and comparators at landmark survival periods. Following this, clinicians were shown extrapolations and asked to confirm which were and were not plausible.

Pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib OS. Hazard ratios were estimated from a comparison of untreated pralsetinib patients in ARROW to untreated advanced wild-type NSCLC patients receiving pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy in the US Flatiron Health EDM dataset. Patients in comparator arms were re-weighted to match key baseline characteristics in the target population as defined by ARROW. Hazard ratios are presented in Table 38. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8).

Table 38: Untreated OS hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)
Pembrolizumab monotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)

CI, confidence intervals; OS, overall survival
Where hazard ratio <1 favours pralsetinib

Figure 34 and Figure 35 display the parametric extrapolations for untreated OS for model comparators which were modelled by applying the respective hazard ratios in Table 38 to pralsetinib.

Figure 34: Parametric extrapolations to model untreated OS for pembrolizumab + pemetrexed + chemotherapy

[redacted]

OS, overall survival

Figure 35: Parametric extrapolations to model untreated OS for pembrolizumab monotherapy

[redacted]

OS, overall survival

Table 39 compares model predictions for OS for all untreated treatment arms at landmark time points against ARROW and range of OS that experts deemed clinically plausible at the advisory board.

Table 39: Validation for model untreated OS at various time points

	1 year			3 years			5 years			10 years			20 years		
	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono	Pral.	Pemb + chem.	Pemb. mono
ARROW	81%	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Expert opinion	--	--	--	50%	30%	25%	40%	10%	8%	10%	3-5%	2%	1%	1%	1%
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival

Clinical experts were first asked to predicted plausible ranges at landmark survival points for pralsetinib and comparators, a task which clinical experts noted the difficulty of in this population. Then clinical experts were shown the extrapolations for pralsetinib and comparators and asked to select the most clinically plausible distributions. The exponential and Weibull distributions were deemed the most clinically plausible by the clinical experts in an advisory board. These two distributions represented the most conservative extrapolations and best represented the clinical experts' plausible landmark survival predictions for pralsetinib. However, both distributions under predicted the clinical experts' plausible landmark survival predictions for pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy. Other distributions predicted closer to clinical expert's landmark survival estimates for comparators but over predicted clinical experts landmark survival predictions for pralsetinib. The Weibull curve demonstrated a decreasing hazard function over time which clinical experts suggested is a characteristic that is observed in this patient population. Therefore, Weibull curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated OS in UK clinical practice and were therefore used in the economic model base-case (Figure 36). This represents a conservative estimate of survival and is in line with clinical expert recommendations. Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 36: Weibull distribution to model untreated OS for pralsetinib and comparators

OS, overall survival

B.3.3.1.2 PFS extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib untreated PFS data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 40 provides the AIC and BIC statistics for pralsetinib.

Table 40: Summary of goodness of fit for untreated PFS – pralsetinib

	PFS – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; PFS, progression-free survival

Based on the AIC values for pralsetinib, the best fitting parametric model for PFS is the log-normal curve. However, given small differences between AIC and BIC values, all parametric models can be considered to show a similar fit. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 37).

Figure 37: Parametric extrapolations to model untreated PFS for pralsetinib

[redacted]

PFS, progression-free survival

A key factor in curve selection was long-term clinically plausibility in the extrapolated period. An advisory board was held to inform long-term clinical plausibility for PFS and assist with curve selected.

Pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib PFS. Hazard ratios were estimated from a comparison of untreated pralsetinib patients in ARROW to untreated advanced wild-type NSCLC patients receiving pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy in the US Flatiron Health dataset. Patients in comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of *RET* fusion-positive patients. Hazard ratios are presented in Table 41. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8).

Table 41: Untreated PFS hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)
Pembrolizumab monotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)

PFS, progression-free survival
Where hazard ratio <1 favours pralsetinib

Figure 38 and Figure 39 display the parametric extrapolations for untreated PFS for model comparators which were modelled by applying the respective hazard ratios in Table 41 to pralsetinib.

Figure 38: Parametric extrapolations to model untreated PFS for pembrolizumab + pemetrexed + chemotherapy

[redacted]

PFS, progression-free survival

Figure 39: Parametric extrapolations to model untreated PFS for pembrolizumab monotherapy

[redacted]

PFS, progression-free survival

Table 42 compares model predictions for PFS for all untreated treatment arms at landmark time points against ARROW and range of PFS that experts deemed clinically plausible at the advisory board.

Table 42: Validation for model untreated PFS at various time points

	1 year			3 years			5 years			10 years			20 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
ARROW	52%	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Expert opinion	--	--	--	30-35%	15%	5%	10-15%	5%	1%	5%	1%	0-1%	1%	1%	0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS, progression-free survival

The exponential distribution was deemed by the clinical experts as the most realistic distribution to model long-term PFS for pralsetinib and comparators. Therefore, the exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated PFS in UK clinical practice and were therefore used in the economic model base-case (Figure 40). Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 40: Exponential distribution to model untreated PFS for pralsetinib and comparators

PFS, progression-free survival

B.3.3.1.3 TTD extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib untreated TTD data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 43 provides the AIC and BIC statistics for pralsetinib.

Table 43: Summary of goodness of fit for untreated TTD – pralsetinib

	TTD – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; TTD, time to treatment discontinuation

Based on the AIC values for pralsetinib, the best fitting parametric model for PFS is the exponential curve. However, given small differences between AIC and BIC values, all parametric models can be considered to show a similar fit. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 41).

Figure 41: Parametric extrapolations to model untreated TTD for pralsetinib

TTD, time to treatment discontinuation

A key factor in curve selection was long-term clinically plausibility in the extrapolated period. An advisory board was held to inform long-term clinical plausibility for TTD and assist with curve selected.

Pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib TTD. Hazard ratios were estimated from a comparison of untreated pralsetinib patients in ARROW to untreated advanced wild-type NSCLC patients receiving pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy in the US Flatiron Health dataset. Patients in comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of *RET* fusion-positive patients. Hazard ratios are presented in Table 44. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8). To reflect UK practice, a stopping rule on pembrolizumab treatment regimens at 2 years was implemented in the model.

Table 44: Untreated TTD hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)
Pembrolizumab monotherapy	[redacted]	Flatiron Health dataset (IPTW) (79)

TTD, time to treatment discontinuation
Where hazard ratio <1 favours pralsetinib

Figure 42 and Figure 43 display the parametric extrapolations for untreated TTD for model comparators which were modelled by applying the respective hazard ratios in Table 44 to pralsetinib. A 2-year stopping rule was applied to pembrolizumab to represent UK clinical practice.

Figure 42: Parametric extrapolations to model untreated TTD for pembrolizumab + pemetrexed + chemotherapy

TTD, time to treatment discontinuation

Figure 43: Parametric extrapolations to model untreated TTD for pembrolizumab monotherapy

TTD, time to treatment discontinuation

Table 45 compares model predictions for TTD for all untreated treatment arms at landmark time points against ARROW and range of TTD that experts deemed clinically plausible at the advisory board.

Table 45: Validation for model untreated TTD at various time points

	1 year			3 years			5 years			10 years			20 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
ARROW	52%	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Expert opinion	--	--	--	30-35%	0%	0%	10-15%	0%	0%	5%	0%	0%	1%	0%	0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: pembrolizumab regimens are assumed to have 0% patients on treatment beyond 2-year stopping rule

TTD, time to treatment discontinuation

For pralsetinib, TTD is likely follow to follow similar trends to PFS. The exponential distribution represents the best fitting distribution to the observed data, was recommended by the clinical experts and maintained consistency with the curve choice for PFS. The exponential curve under-predicts the clinical expert's landmark TTD prediction at 3 years ([redacted] vs 30-35%). However, the clinical experts noted difficulty at this task for this patient population. The exponential curve does accurately predict TTD in the ARROW trial at 2 years ([redacted] vs [redacted]). Therefore, exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated TTD in UK clinical practice and were therefore used in the economic model base-case (Figure 44). Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 44: Exponential distribution to model untreated TTD for pralsetinib and comparators

[redacted]

TTD, time to treatment discontinuation

B.3.3.2 Pre-treated

B.3.3.2.1 OS extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib pre-treated OS data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 46 provides the AIC and BIC statistics for pralsetinib.

Table 46: Summary of goodness of fit for pre-treated OS – pralsetinib

	OS – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; OS, overall survival

Based on the AIC values for pralsetinib, the best fitting parametric model for OS is the generalised gamma curve. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 45).

Figure 45: Parametric extrapolations to model pre-treated OS for pralsetinib

[redacted]

OS, overall survival

A key factor in curve selection was long-term clinically plausibility in the extrapolated period. An advisory board was held to inform long-term clinical plausibility for OS and assist with curve selected.

Docetaxel monotherapy, docetaxel + nintedanib and platinum-based chemotherapy +/- pemetrexed were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib OS. Hazard ratios were estimated from comparing pre-treated pralsetinib patients in ARROW to available published studies of wild type advanced NSCLC patients. Patients in the comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of *RET* fusion-positive patients where possible. Hazard ratios are presented in Table 47. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8).

Table 47: Pre-treated OS hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Docetaxel monotherapy	[redacted]	OAK trial (propensity scoring IPTW (77)
Docetaxel + nintedanib	[redacted]	LUME-Lung 1 (naïve comparison) (57)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison) (78)

OS, overall survival
Where hazard ratio <1 favours pralsetinib

Figure 46 and Figure 48 display the parametric extrapolations for pre-treated OS for model comparators which were modelled by applying the respective hazard ratios in Table 47 to pralsetinib.

Figure 46: Parametric extrapolations to model pre-treated OS for docetaxel monotherapy

[redacted]
OS, overall survival

Figure 47: Parametric extrapolations to model pre-treated OS for docetaxel + nintedanib

[redacted]
OS, overall survival

Figure 48: Parametric extrapolations to model pre-treated OS for platinum-based chemotherapy +/- pemetrexed

[redacted]
OS, overall survival

Table 47 compares model predictions for OS for all pre-treated treatment arms at landmark time points against ARROW and range of OS that experts deemed clinically plausible at the advisory board.

Table 48: Validation for model pre-treated OS at various time points

	3 years				5 years				10 years				20 years			
	Pral	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**
Expert opinion	35%	5%	5%	15%	20%	2%	2%	5%	7%	0%	0%	1%	1%	0%	0%	0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival, PBC, platinum-based chemotherapy

In the advisory board, the clinical experts agreed that the proportion of patients alive after second-line treatment with pralsetinib should be slightly lower than the estimates for first-line treatment due to the difference in available subsequent treatments, and the likelihood of more patients with CNS metastases. Clinical experts agreed that they did not expect to see a notable difference in OS between docetaxel monotherapy and docetaxel + nintedanib patients. Clinical experts agreed that the more optimistic log-logistic, log-normal, Gompertz and generalised gamma distributions appeared to be clinically implausible and the more conservative exponential and Weibull curves were likely to better represent OS. In this instance, the Weibull curve demonstrated an increasing hazard of mortality over time which was not thought to be clinically plausible. The exponential curve over-predicts the clinical expert's landmark OS prediction at 3 years ([redacted] vs 35%). However, the clinical experts noted difficulty at this task for this patient population. The exponential curve does slightly under-predict OS in the ARROW trial at 2 years ([redacted] vs [redacted]). The exponential curve aligns with the clinical experts expectation of median OS for docetaxel monotherapy in this population from the selpercatinib appraisal ([redacted] months vs 9-10 months) (71). Therefore, exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator pre-treated OS in UK clinical practice and were therefore used in the economic model base-case (Figure 49). Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 49: Exponential distribution to model pre-treated OS for pralsetinib and comparators

[redacted]

OS, overall survival

B.3.3.2.2 PFS extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib pre-treated PFS data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 49 provides the AIC and BIC statistics for pralsetinib.

Table 49: Summary of goodness of fit for pre-treated PFS – pralsetinib

	PFS – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; PFS, progression-free survival

Based on the AIC values for pralsetinib, the best fitting parametric model for PFS is the generalised gamma curve. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 50).

Figure 50: Parametric extrapolations to model pre-treated PFS for pralsetinib

[redacted]

PFS, progression-free survival

A key factor in curve selection was long-term clinically plausibility in the extrapolated period. An advisory board was held to inform long-term clinical plausibility for PFS and assist with curve selected.

Docetaxel monotherapy, docetaxel + nintedanib and platinum-based chemotherapy +/- pemetrexed were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib PFS. Hazard ratios were estimated from comparing pre-treated pralsetinib patients in ARROW to available published studies of wild type advanced NSCLC patients. Patients in the comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of *RET* fusion-positive patients where possible. Hazard ratios are presented in Table 50. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8).

Table 50: Pre-treated PFS hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Docetaxel monotherapy	[redacted]	OAK trial (propensity scoring IPTW) (77)
Docetaxel + nintedanib	[redacted]	Assumed equal to docetaxel monotherapy
Platinum-based chemotherapy +/- pemetrexed	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison) (78)

PFS, progression-free survival
Where hazard ratio <1 favours pralsetinib

Figure 51-Figure 53 display the parametric extrapolations for pre-treated PFS for model comparators which were modelled by applying the respective hazard ratios in Table 50 to pralsetinib.

Figure 51: Parametric extrapolations to model pre-treated PFS for docetaxel monotherapy

[redacted]

PFS, progression-free survival

Figure 52: Parametric extrapolations to model pre-treated PFS for docetaxel + nintedanib

[redacted]

PFS, progression-free survival

Figure 53: Parametric extrapolations to model pre-treated PFS for platinum-based chemotherapy +/- pemetrexed

[redacted]

PFS, progression-free survival

Table 51 compares model predictions for PFS for all pre-treated treatment arms at landmark time points against ARROW and range of PFS that experts deemed clinically plausible at the advisory board.

Table 51: Validation for model pre-treated PFS at various time points

	3 years				5 years				10 years				20 years			
	Pral	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**
Expert opinion	30-35%	1-2%	1-2%	5%	10-15%	0%	0%	1%	5%	0%	0%	0%	1%	0%	0%	0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PBC, platinum-based chemotherapy, PFS, progression-free survival

Clinical experts at an advisory board suggested that the generalised gamma, gamma and Gompertz distributions were not clinically plausible. In this instance, the Weibull curve demonstrated an increasing hazard of mortality over time which was not thought to be clinically plausible. Therefore, exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator pre-treated PFS in UK clinical practice and were therefore used in the economic model base-case (Figure 54). Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 54: Exponential distribution to model pre-treated PFS for pralsetinib and comparators

[redacted]

PFS, progression-free survival

B.3.3.2.3 TTD extrapolation

To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (exponential, Weibull, log-normal, generalised gamma, log-logistic, gamma and Gompertz) were fitted to the observed pralsetinib pre-treated TTD data and assessed for goodness of fit using AIC and BIC tests, and visual inspection. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 52 provides the AIC and BIC statistics for pralsetinib.

Table 52: Summary of goodness of fit for pre-treated TTD – pralsetinib

	TTD – goodness of fit statistics pralsetinib	
Parametric distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

AIC, Akaike information criterion; BIC Bayesian information criterion; TTD, time to treatment discontinuation

Based on the AIC values for pralsetinib, the best fitting parametric model for TTD is the log-normal curve. All parametric models were assessed for visual fit to the Kaplan-Meier data (Figure 55).

Figure 55: Parametric extrapolations to model pre-treated TTD for pralsetinib

TTD, time to treatment discontinuation

A key factor in curve selection was long-term clinically plausibility in the extrapolated period. An advisory board was held to inform long-term clinical plausibility for TTD and assist with curve selected.

Docetaxel monotherapy, docetaxel + nintedanib and platinum-based chemotherapy +/- pemetrexed were modelled by applying a hazard ratio from the indirect treatment comparison (Section B.2.9) to the modelled pralsetinib TTD. Hazard ratios were estimated from comparing pre-treated pralsetinib patients in ARROW to available published studies of wild type advanced NSCLC patients. Patients in the comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of *RET* fusion-positive patients where possible. In studies from the published literature, TTD was not reported and therefore a hazard ratio vs. pralsetinib was not able to be calculated. Therefore, an assumption was made that the hazard ratio on TTD was equal for the hazard ratio for PFS for pralsetinib vs. each comparator respectively. Hazard ratios are presented in Table 53. Varying assumptions for hazard ratios are explored in the sensitivity analysis (Section B.3.8).

Table 53: Pre-treated TTD hazard ratios for pralsetinib vs. comparator treatments

	Hazard ratio of pralsetinib vs. comparator treatments (95% CI)	Source
Docetaxel monotherapy	[redacted]	OAK trial (propensity scoring IPTW; assumed equal to PFS) (77)
Docetaxel + nintedanib	[redacted]	Assumed equal to docetaxel monotherapy
Platinum-based chemotherapy +/- pemetrexed	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison; assumed equal to PFS) (78)

PFS, progression-free survival, TTD, time to treatment discontinuation
Where hazard ratio <1 favours pralsetinib

Figure 56-Figure 58 display the parametric extrapolations for pre-treated TTD for model comparators which were modelled by applying the respective hazard ratios in Table 53 to pralsetinib.

Figure 56: Parametric extrapolations to model pre-treated TTD for docetaxel monotherapy

TTD, time to treatment discontinuation

Figure 57: Parametric extrapolations to model pre-treated TTD for docetaxel + nintedanib

TTD, time to treatment discontinuation

Figure 58: Parametric extrapolations to model pre-treated TTD for platinum-based chemotherapy +/- pemetrexed

TTD, time to treatment discontinuation

Table 54 compares model predictions for TTD for all pre-treated treatment arms at landmark time points against ARROW and range of TTD that experts deemed clinically plausible at the advisory board.

Table 54: Validation for model pre-treated TTD at various time points

	3 years				5 years				10 years				20 years			
	Pral	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**
Expert opinion	30-35%	0%	0%	1%	10-15%	0%	0%	0%	5%	0%	0%	0%	1%	0%	0%	0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PBC, platinum-based chemotherapy, TTD, time to treatment discontinuation

The generalised gamma, Gompertz, log-logistic and log-normal distributions are thought to over predict long-term TTD for pralsetinib with [redacted] of patients estimated to still be on treatment after 10 years in these distributions. The exponential and Weibull distributions provide the most clinically plausible landmark TTD aligned to the clinical experts' plausible ranges for pralsetinib and comparators. The exponential distribution maintains consistency with PFS. Therefore, exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator pre-treated TTD in UK clinical practice and were therefore used in the economic model base-case (Figure 59). Alternative curve choices were investigated in the scenario analysis (Section B.3.8.3).

Figure 59: Exponential distribution to model pre-treated TTD for pralsetinib and comparators

[redacted]

TTD, time to treatment discontinuation

B.3.3.3 Adverse events

Adverse events for pralsetinib were sourced from the ARROW trial safety population. The ITT population in ARROW was used which contained subjects not exclusive to NSCLC and subjects on all doses (n=404). Adverse events for comparators were taken from the available literature. All grade ≥3 adverse events with an incidence of ≥2% in at least one treatment arm were included in the economic model. Adverse events included in the model are shown in Table 55 below. Section B.3.4.5 contains further information on the inclusion of disutilities associated with adverse events and Section B.3.5.2 contains further information on the inclusion of costs associated with adverse events.

Table 55: Adverse events included in the economic model

	Untreated			Pre-treated			
n, (%)	Pral	Pembro + chemo	Pembro mono	Pral	Doce mono	Doce + nin	PBC +/- pem
	ARROW	(75)	(76)	ARROW	(77)	(57)	(78)
	n=404	n=405	n=636	n=404	n=578	n=652	n=287
Anaemia	[redacted]	74 (18)	0 (0)	52 (13)	33 (6)	0 (0)	0 (0)
Asthenia	[redacted]	27 (7)	0 (0)	7 (2)	13 (2)	13 (2)	10 (3)
Blood creatinine phosphokinase increased	[redacted]	0 (0)	0 (0)	12 (3)	0 (0)	0 (0)	0 (0)
Decreased appetite	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)
Decreased neutrophils	[redacted]	0 (0)	0 (0)	20 (5)	0 (0)	209 (32)	0 (0)
Decreased white blood cell count	[redacted]	0 (0)	0 (0)	17 (4)	0 (0)	107 (16)	0 (0)
Diarrhoea	[redacted]	21 (5)	0 (0)	16 (4)	0 (0)	43 (7)	0 (0)
Disease progression	[redacted]	0 (0)	0 (0)	11 (3)	0 (0)	0 (0)	0 (0)
Dyspnoea	[redacted]	17 (4)	0 (0)	10 (2)	14 (2)	32 (5)	14 (5)
Fatigue	[redacted]	28 (7)	0 (0)	11 (3)	23 (4)	37 (6)	9 (3)
Febrile neutropenia	[redacted]	0 (0)	0 (0)	0 (0)	62 (11)	46 (7)	0 (0)
Hepatitis	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)
Hypertension	[redacted]	0 (0)	0 (0)	57 (14)	0 (0)	0 (0)	0 (0)
Hypocalcaemia	[redacted]	0 (0)	0 (0)	12 (3)	0 (0)	0 (0)	0 (0)
Hyponatraemia	[redacted]	0 (0)	0 (0)	17 (4)	0 (0)	14 (2)	0 (0)
Hypophosphataemia	[redacted]	0 (0)	0 (0)	21 (5)	0 (0)	0 (0)	0 (0)
Increased ALT	[redacted]	0 (0)	0 (0)	14 (3)	0 (0)	51 (8)	0 (0)
Increased AST	[redacted]	0 (0)	0 (0)	22 (5)	0 (0)	22 (3)	0 (0)
Leukopenia	[redacted]	0 (0)	0 (0)	8 (2)	0 (0)	19 (3)	0 (0)
Lymphocyte count decreased	[redacted]	0 (0)	0 (0)	24 (6)	0 (0)	0 (0)	0 (0)
Lymphopenia	[redacted]	0 (0)	0 (0)	19 (5)	0 (0)	0 (0)	0 (0)
Malignant neoplasm progression	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	14 (5)
Nausea	[redacted]	14 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neutropenia	[redacted]	65 (16)	0 (0)	42 (10)	75 (13)	79 (12)	0 (0)
Pain	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (2)
Pleural effusion	[redacted]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)
Pneumonia	[redacted]	0 (0)	47 (7)	33 (8)	0 (0)	20 (3)	10 (3)
Pneumonitis	[redacted]	12 (3)	0 (0)	11 (3)	0 (0)	0 (0)	0 (0)
Rash	[redacted]	8 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sepsis	[redacted]	0 (0)	0 (0)	13 (3)	0 (0)	0 (0)	0 (0)
Severe skin reactions	[redacted]	9 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	[redacted]	34 (8)	0 (0)	9 (2)	0 (0)	0 (0)	0 (0)
Urinary tract infection	[redacted]	0 (0)	0 (0)	12 (3)	0 (0)	0 (0)	0 (0)
Vomiting	[redacted]	16 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

B.3.4 Measurement and valuation of health effects

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

EuroQol 5 Dimensions (EQ-5D) was not collected in ARROW. Rather, the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) was used to obtain HRQoL data, collected directly from *RET* fusion-positive NSCLC subjects. The EORTC QLQ-C30 is a 30-item questionnaire used to evaluate HRQoL. It includes five functional domains (physical, cognitive, role, emotional and social), a global health status scale and symptom scales/items. Each subscale was evaluated on a standardised scale of 0 to 100. EuroQol 5 Dimensions (EQ-5D) was not collected in ARROW.

EORTC QLQ-C30 scoring were required to be collected for patients enrolled on or after Protocol Amendment 7 during Phase 2 where the starting dose for all patients was 400 mg QD. Patients completed the EORTC QLQ-C30 on Day 1 of Cycles 1 through 12. If the patient did not complete the questionnaire at Cycle 1 Day 1 (i.e., for a baseline), they were asked not to complete the questionnaire at subsequent cycles. In total, 74.7% (210/281) of subjects in the unrestricted efficacy population returned an EORTC QLQ-C30 response at baseline and 69.0% (194/281) returned a response at baseline and had at least one further post-baseline assessment available.

Overall, the median (range) EORTC QLQ-C30 global health status score in patients with RET fusion–positive NSCLC was 83.0 (75 to 100) out of 100 possible points at the last assessment (Week 48), with minimal changes (≤16 points) from baseline observed at all time points over a duration of 48 weeks.

High mean and median scores have been reported for physical, role, emotional, cognitive, and social functioning indicating a high level of functioning, with minimal changes from baseline observed at all time points (mostly <10 points change from baseline). At baseline, patients reported low levels of clinical symptoms, which remained low with little changes throughout all time points. From baseline to last assessment, there was a tendency toward less pain and insomnia (change of ≤16 points) and toward more constipation (consistent with what was seen for AE reporting). Low mean and median scores were observed for the financial difficulties scale, with no relevant changes from baseline observed at all time points.

B.3.4.2 Mapping

Roche explored the feasibility of mapping from EORTC QLQ-C30 to EQ-5D-3L in order to inform utilities for the economic model that were informed by ARROW clinical trial data. A multinomial logistic regression approach as described by Longworth et al. was used (97). Across both the 210 subjects in the untreated and pre-treated patient populations for the PF and PD health states a

mean utility value of 0.741 (SD 0.228; median 0.804) was estimated. However, given the large amount of missing data, utilities were not viewed as robust enough to inform decision making. Therefore, health state utility values from the literature (Sections B.3.4.3-5) were preferred.

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

A SLR was conducted to identify HRQoL evidence in the treatment of patients with *RET* fusion-positive NSCLC. A review was carried out on 09 October 2020 to identify studies in *RET* fusion-positive NSCLC that included published economic evaluations.

Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H. No studies were identified which reported utility data associated specifically with patients with *RET* fusion-positive NSCLC.

Due to the paucity of health state utility value data in the population of interest, previous NICE appraisals were hand searched in order to identify the most relevant health state utility values to inform the current economic model. Given the similarities between the current appraisal and ID3743, health state utility values proposed in ID3743 (following ERG recommendation) have been included in this appraisal. In the absence of *RET* fusion-positive health state utility data, it is assumed that *RET* fusion-positive patients do no demonstrate different HRQoL from advanced NSCLC patients and therefore advanced NSCLC health state utility values can be used. This assumption has been validated by clinical experts. A summary of utilities identified that met the requirements of the NICE reference case is provided in Table 56.

Table 56: Summary of utility values for cost-effectiveness analysis

Source	Health state utilities		Justification
	PF	PD	
Untreated			
TA654 (base case) (98)	0.794	0.678	Given similarities between patient populations, EGFR-positive advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.
TA310 (scenario) (99)	0.784	0.725	Given similarities between patient populations, ALK-positive advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.
TA643 (scenario) (100)	0.780	0.660	Given similarities between patient populations, ROS1-positive advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.
Pre-treated			

TA713, ID3743 (base case) (71, 101)	0.713	0.628	Given similarities between patient populations, advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.
TA653 (scenario) (102)	0.853	0.659	Given similarities between patient populations, EGFR-positive advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.
TA310 (scenario) (99)	0.672	0.653	Given similarities between patient populations, ALK-positive advanced NSCLC patients could be considered a suitable proxy for *RET* fusion-positive patients. Utilities were approved by ERG and Committee in appraisal.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ERG, Evidence Review Group; NSCLC, non-small cell lung cancer; PD, progressed disease; PF, progression-free

B.3.4.4 Adverse reactions

All grade ≥3 adverse events, with an incidence of ≥2% in at least one treatment arm were included in the economic model.

As identical health state utility values are used in each treatment arm of the economic model, variations in HRQoL between treatments associated with adverse events have been implemented in the model by calculating a QALY loss associated with each adverse event. The loss of QALYs per adverse event was calculated as the product of the utility decrement and the duration of the adverse event. Disutilities were sourced from the available published literature. A summary of the adverse events and QALY losses included in the economic model is provided in Table 57. QALY loss associated with adverse events were applied in the first cycle of the model.

Table 57: Summary of adverse events and disutilities included in the economic model (events occurring at Grade 3-5, affecting 2% or more of patients)

Adverse event	Disutility	Days	QALY loss	Source
Anaemia	-0.074	23.8	-0.005	NICE TA713 (101); Disutility: Nafees et al., 2008 (103); Duration: Assumption (same as fatigue)
Asthenia	-0.074	23.8	-0.005	NICE TA713 (101); Disutility: Nafees et al., 2008 (103); Duration: Assumption (same as fatigue)
Blood creatinine phosphokinase increased	0.000	0.0	0.000	No data available
Decreased appetite	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption

Decreased neutrophils	0.000	0.0	0.000	Assumption
Decreased white blood cell count	-0.050	15.0	-0.002	NICE TA713 (101); Duration: Assumption
Diarrhoea	-0.047	5.5	-0.001	NICE TA261 (105); Disutility: Nafees et al., 2008 (103); Duration: NICE TA476 (Study CA046)
Disease progression	0.000	0.0	0.000	Not applicable
Dyspnoea	-0.050	15.0	-0.002	NICE TA713 (101); Disutility: Doyle et al., 2008 (106); Duration: Assumption
Fatigue	-0.074	23.8	-0.005	NICE TA261 (105); Disutility: Nafees et al., 2008 (103); Duration: NICE TA306 (PIX301) (107), NICE TA476 (Study CA046) (108)
Febrile neutropenia	-0.090	15.0	-0.004	NICE TA428, Table 10 (104); Disutility: Nafees et al., 2008 (103); Duration: Assumption
Hepatitis	0.000	0.0	0.000	Assumption
Hyperglycaemia	0.000	0.0	0.000	No data available
Hypertension	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Hypocalcaemia	0.000	0.0	0.000	No data available
Hyponatraemia	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Hypophosphataemia	0.000	0.0	0.000	No data available
Increased ALT	0.000	0.0	0.000	No data available
Increased AST	0.000	0.0	0.000	No data available
Leukopenia	-0.0897	15.0	-0.0037	NICE TA713 (101); Duration: Assumption
Lymphocyte count decreased	0.000	0.0	0.000	No data available
Lymphopenia	-0.050	15.0	-0.002	NICE TA713 (101); Disutility: TA449 (109); Duration: Assumption
Malignant neoplasm progression	0.000	0.0	0.000	Not applicable
Nausea	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Neutropenia	-0.090	15.0	-0.004	NICE TA428, Table 10 (104); Disutility: Nafees et al., 2008 (103); Duration: Assumption

Pain	0.000	0.0	0.000	No data available
Pleural effusion	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Pneumonia	-0.008	15.0	0.000	NICE TA713 (101); Disutility: Marti et al., 2013 (110); Duration: Assumption
Pneumonitis	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Rash	0.000	0.0	0.000	No data available
Sepsis	-0.090	15.0	-0.004	Assumed same as febrile neutropenia
Severe skin reactions	0.000	0.0	0.000	Assumption
Thrombocytopenia	0.000	0.0	0.000	Assumption
Urinary tract infection	-0.085	15.0	-0.003	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption
Vomiting	0.000	15.0	0.000	NICE TA428; Disutility: KEYNOTE-010 (TA428) (104); Duration: Assumption

ALT, alanine aminotransferase; AST, aspartate aminotransferase; QALY, quality-adjusted life year

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

A summary of utility values used in the economic model is provided in Table 58.

Table 58: Summary of utility values for cost-effectiveness analysis

State	Utility/ QALY loss	Reference in submission	Justification
Health state utility values: untreated			
PF	0.794	Section B.3.4.3	As used in ID3743; TA654 (71, 98)
PD	0.678	Section B.3.4.3	As used in ID3743; TA654 (71, 98)
Health state utility values: pre-treated			
PF	0.713	Section B.3.4.3	As used in ID3743; TA713 (71, 101)
PD	0.628	Section B.3.4.3	As used in ID3743; TA713 (71, 101)
Adverse event QALY loss			
All adverse events	As per Table 57	Section B.3.4.4	Taken from previously published literature

PD, progressed disease; PF, progression-free; QALY, quality-adjusted life year

As the model time horizon is 25 years, it is important to consider the impact of age and sex-related disutility. A multiplicative approach to utilities was assumed. The regression algorithm from Ara and Brazier 2010 (111) was used to generate utility multipliers to decrease baseline utility as patient's age within the model. Model baseline age was assumed to be equivalent to baseline age in

ARROW (untreated: 63.0 years; pre-treated: 59.5 years). The proportion of males (49.7%) from ARROW was assumed. Table 59 demonstrates the impact of the age and sex adjustment from the Ara and Brazier algorithm on model health state utility values by model year.

Table 59: Impact of age and sex adjustment on health state utilities

Model year	Patient age	General population utility	PF multiplier	PF utility	PD multiplier	PD utility
Untreated						
0	63	0.814	97.7%	0.794	83.4%	0.678
1	64	0.810	97.7%	0.790	83.4%	0.675
…	…	…	…	…	…	…
25	88	0.682	97.7%	0.665	83.4%	0.568
Pre-treated						
0	59	0.830	85.9%	0.713	68.5%	0.628
1	60	0.825	85.9%	0.709	68.5%	0.625
…	…	…	…	…	…	…
25	84	0.705	85.9%	0.605	68.5%	0.533

PD, progressed disease; PF, progression-free

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

An SLR was conducted to identify studies presenting novel cost and resource use data associated with *RET* fusion-positive NSCLC, relevant to the economic model presented herein. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix I.

The electronic database searches identified a total of 2,397 citations. Following removal of 518 duplicates, 1,879 citations were screened on the basis of title and abstract. A total of ten citations were considered to be potentially relevant and were obtained for full text review. At this stage, a further nine citations were excluded. Hand searching yielded no additional relevant articles for inclusion. Therefore, one published study was identified for final inclusion in the cost/resource use SLR.

A single published study was identified for inclusion in the cost/resource use SLR (112); the study explored incremental testing costs associated with tissue-based next generation sequencing in Canada with incremental testing costs based on direct laboratory costs, but not personnel and administration costs. The study was presented as a conference abstract only and formal quality assessment was therefore not conducted. The study was not considered to be relevant to the decision problem and not considered to reflect current UK clinical practice. Therefore, costs and resource use are based on available evidence in previous NICE submissions.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs for the treatments included in the economic model are summarised in Table 60. For medicines available to the NHS as generic medicines, prices are taken from the electronic market information tool (eMIT), which reports the average price paid by the NHS for a generic medicine for the last period (113). For medicines only available to the NHS as proprietary medicines, prices are taken as the list price stated in the British National Formulary (BNF) (114). For pralsetinib, a patient access scheme (PAS) is included which offers a discount of [redacted]. All other treatments are assumed to be at list price. For regimens including either cisplatin or carboplatin, a 50:50 split of cisplatin and carboplatin is assumed in line with clinical expert opinion. For pre-treated treatment with platinum-based chemotherapy +/- pemetrexed, no other platinum-based chemotherapies were included in the costings given the minimal impact of differences in acquisition costs of platinum-based chemotherapies on model results and that cisplatin/carboplatin are the most commonly used. Further, for platinum-based chemotherapy +/- pemetrexed, it was assumed that 63% of patients received pemetrexed. This assumption is in line with clinical guidance to reflect UK clinical practice. This is a conservative assumption as in the patient population in the study that informed the efficacy for platinum-based chemotherapy +/- pemetrexed in the indirect comparison, 100% of patients received pemetrexed.

Table 60: Treatment acquisition costs

Line	Regimen	Drug	Pack size	Price per pack (£)	Cost per month	Source
Untreated	Pralsetinib	Pralsetinib (list price)	120 x 100mg	7,044.00	7,146.73	--
		Pralsetinib (PAS price)	120 x 100mg	[redacted]	[redacted]	--
	Pembrolizumab + pemetrexed + chemotherapy	Pembrolizumab	1 x 100mg	2,630.00	7,623.87	BNF
		Pemetrexed	1 x 100mg	160.00	2,029.17	BNF
		Cisplatin	1 x 100mg	8.73	16.61	eMIT
		Carboplatin	1 x 450mg	13.76	31.02	eMIT
	Pembrolizumab monotherapy	Pembrolizumab	1 x 100mg	2,630.00	7,623.87	BNF
Pre-treated	Pralsetinib	Pralsetinib (list price)	120 x 100mg	7,044.00	7,146.73	--
		Pralsetinib	120 x 100mg	[redacted]	[redacted]	--

		(PAS price)				
	Docetaxel	Docetaxel	1 x 160mg	17.95	21.34	eMIT
	Docetaxel + nintedanib	Docetaxel	1 x 160mg	17.95	21.34	eMIT
		Nintedanib	120 x 100mg	2,151.10	2,078.54	BNF
	Platinum-based chemotherapy +/- pemetrexed	Pemetrexed	1 x 100mg	160.00	2,029.17	BNF
		Cisplatin	1 x 100mg	8.73	4.43	eMIT
		Carboplatin	1 x 450mg	13.76	31.02	eMIT

BNF, British National Formulary; eMIT, electronic market information tool

B.3.5.1.2 Drug administration costs

Table 61 provides the administration costs assumed for the intervention and comparators.

Table 61: Administration costs

Line	Regimen	Drug	Type of admin.	Cost per first admin. (£)	Cost per subsequent admin. (£)	Source
Untreated	Pralsetinib	Pralsetinib	Oral	195.00	15.00	NHS SB11Z; TA643 12 mins pharmacist time
	Pembrolizumab + pemetrexed + chemotherapy	Pembrolizumab	IV	370.68	332.13	NHS ref. SB14Z, SB15Z
		Pemetrexed				
		Cisplatin				
		Carboplatin				
	Pembrolizumab monotherapy	Pembrolizumab	IV	241.06	241.06	NHS ref. SB12Z
Pre-treated	Pralsetinib	Pralsetinib	Oral	195.00	15.00	NHS SB11Z; TA643 12 mins pharmacist time
	Docetaxel	Docetaxel	IV	241.06	241.06	NHS ref. SB12Z
	Docetaxel + nintedanib	Docetaxel	IV	241.06	241.06	NHS ref. SB12Z
		Nintedanib	Oral	195.00	15.00	NHS SB11Z; TA643 12 mins pharmacist time

	Platinum-based chemotherapy +/- pemetrexed	Pemetrexed	IV	370.68	332.13	NHS ref. SB14Z, SB15Z
		Cisplatin				
		Carboplatin				

NHS, National Health Service

Source: NHS reference costs 2018/19, PSSRU 2020 (115, 116)

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Supportive care costs

Supportive care costs are applied for both PF, and PD health states. The types of resource and frequency of use are derived from previous line-agnostic advanced NSCLC technology appraisals (TA643, as accepted by the ERG). Unit costs were derived from NHS reference costs and PSSRU (115, 116). Table 62 detail the resource use for PF and PD health states respectively for the untreated and pre-treated analyses. The monthly cost of supportive care is £200.26 in the PF health state and £222.13 in the PD health state. These costs are applied for each cycle a patient is alive in the PF or PD health state in both the untreated and pre-treated economic analyses.

There is considerable extra cost burden if a patient progresses in the CNS. Therefore, it is anticipated that CNS patients will incur additional PD supportive care costs (117). Pralsetinib penetrates the blood–brain barrier and is efficacious in brain metastases: an intracranial ORR rate of [redacted] was observed in ten patients with measurable CNS metastases (Table 19). Therefore, pralsetinib may reduce PD supportive care costs in CNS patients compared to comparators. However, given ARROW was a single arm trial, it was not possible estimate the rate of reduction of CNS in patients in pralsetinib arms compared to comparators and therefore include the potential cost savings in the economic model.

Table 62: Supportive care resource use and costs for the PF and PD health state (untreated and pre-treated analysis)

Resource	Freq. per model cycle (PF)	Freq. per model cycle (PD)	Unit cost (£)	Total cost per model cycle (£, PF)	Total cost per model cycle (£, PD)	Source
Outpatient visit	0.75	1.00	192.90	144.68	192.90	Outpatient medical oncology 370
GP visit	0.10	0.28	33.00	3.30	9.24	Clinical consultation 9.22 minutes
Cancer nurse	0.20	0.10	91.24	18.25	9.12	N10AF

Complete blood count	0.75	1.00	2.58	1.94	2.58	DAPS05
Biochemistry	0.75	1.00	1.22	0.92	1.22	DAPS04
CT scan	0.23	0.04	111.58	25.66	4.46	RD26Z
Chest X-ray	0.23	0.23	32.53	7.48	7.48	DAPF
Total cost per model cycle length				**202.22**	**227.01**	

CT, computerised tomography; GP: general practitioner; PD, progressed disease; PF, progression-free

Source: TA643, NHS reference costs 2018/19, PSSRU 2020 (100, 115, 116)

B.3.5.2.2 Terminal care costs

Terminal care / end-of-life costs are detailed in Table 63. A terminal care/end-of-life cost is applied to patients who enter the death state as a one-off cost, in line with a previous line-agnostic advanced NSCLC technology appraisal (TA643, as accepted by the ERG (100, 118)). This cost is assumed equal in each treatment arm. The total cost of end-of-life is £7,594.42.

Table 63: Resource use for terminal care / end-of-life

Resource	Cost (£)	Source
District nurse	306.96	Taken from Georghiou and Bardsley, updated to 2020 costs using PSSRU 2020 (115, 118)
Nursing and residential care	1,104.16	
Hospital care-inpatient	607.29	
Hospital care - final 3 months of life	4,968.72	
Marie Curie nursing service	607.29	
Total terminal care / end-of-life cost per patient	**7,594.42**	

PSSRU, Personal Social Services Research Unit

B.3.5.3 Adverse reaction unit costs and resource use

All grade ≥3 treatment-related adverse events with an incidence of ≥2% are included in the base-case analysis.

Adverse event unit costs were sourced from previous NICE appraisals in NSCLC where possible. Where this was not possible, the NHS HRG code grouper was used (119). The code grouper uses ICD-10 codes for diseases and indicates which HRG code they are assigned to. NHS reference costs were then used to identify unit costs for all relevant HRG codes.

The cost of adverse events for each treatment arm is calculated by multiplying the incidence of each adverse event and its unit cost. Adverse event costs are applied as a one-off cost in the first cycle of treatment only, hence it is assumed that the adverse event occurs at treatment initiation, only once across the time horizon of the model.

The probability of patients experiencing each adverse event are provided in Table 55, while the resources and associated costs are described in Table 64. Table 65 shows the total adverse even cost by treatment arm.

Table 64: Resources associated with adverse events

Adverse Event	ICD-10 Code	Source/HRG codes used from reference costs	Unit costs
Anaemia	--	SA04L (116, 120)	£341.86
Asthenia	R53X	WH17C	£345.17
Blood creatinine phosphokinase increased	--	Assumed (121)	£0
Decreased appetite	--	Assumed (121)	£0
Decreased neutrophils	--	Assumed (122)	£0
Decreased white blood cell count	--	Assumed (122)	£0
Diarrhoea	--	Assumed (122)	£0
Disease progression	--	Assumed	£0
Dyspnoea	--	(115, 122)	£484.66
Fatigue	R53X	(115, 122)	£3,030.35
Decreased white blood cell count	--	Assumed (122)	£0
Hepatitis	B179	GC17K	£345.17
Hyperglycaemia	R739	WH13C	£598.58
Hypertension	I10X	EB04Z	£486.45
Hypocalcaemia	E835	KC05N	£486.45
Hyponatraemia	E871	KC05N	£192.77
Hypophosphataemia	--	Assumed (121)	£0
Increased ALT	--	Assumed (122)	£0

Increased AST	--	(115, 122)	£367.68
Leukopenia	--	(120)	£0
Lymphocyte count decreased	D728	SA08J	£618.08
Lymphopenia	D728	SA08J	£697.47
Malignant neoplasm progression	C349	DZ17V	£811.60
Nausea	--	(115, 122)	£1,059.60
Neutropenia	D70X	(115, 122)	£625.11
Pain	R520	WH08B	£741.69
Pleural effusion	J90X	DZ16R	£926.57
Pneumonia	--	Assumed (122)	£655.53
Pneumonitis	J69.8	DZ24R	£534.34
Rash	--	Assumed (122)	£0
Sepsis	A419	WJ06J	£534.34
Severe skin reactions	R21X	JD07K	£419.50
Thrombocytopenia	--	(115, 122)	£128.41
Urinary tract infection	--	(122)	£135.01
Vomiting	--	(122)	£980.87

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHS, National Health Service

Table 65: Total adverse event costs per treatment arm

Line	Regimen	Total adverse events costs (£)
Untreated	Pralsetinib	[redacted]
	Pembrolizumab + pemetrexed + chemotherapy	526.96
	Pembrolizumab monotherapy	48.44
Pre-treated	Pralsetinib	[redacted]
	Docetaxel	240.72
	Docetaxel + nintedanib	315.03
	Platinum-based chemotherapy +/-	245.83

	pemetrexed	

The cost of adverse events for each treatment arm is calculated by multiplying the incidence of each adverse event and its unit cost

B.3.5.4 Subsequent treatment costs

The economic model includes costs and resource use of subsequent treatment for patients who have progressed after first-line treatment with pralsetinib, or the relevant comparators. To reflect UK clinical practice, upon progression patients are modelled to receive subsequent treatments. The distribution of subsequent treatments is multiplied by the acquisition and administration costs of each subsequent treatment and the duration of time on subsequent treatments. Subsequent treatment costs are applied as a one-off cost in the economic model when patients enter the PD health state. Those patients who are not modelled to receive a subsequent treatment are modelled to receive best supportive care, which is not associated with additional cost.

B.3.5.4.1 Distribution of subsequent treatments

The distribution of subsequent treatments that accurately reflects UK practice was estimated via expert opinion with key clinical UK experts in an advisory board to inform the model base-case. Treatment duration was estimated from the available published literature. The subsequent treatments after first-line treatment are shown in Table 66. The proportion of patients receiving subsequent treatment in UK clinical practice was estimated via expert opinion.

Following treatment in second-line, a high proportion of patients receive best supportive care. For those that do receive treatment, treatment tends to be with generically available treatments. There is not anticipated to be a substantial difference in the difference of subsequent treatments (and therefore costs) received following pralsetinib and comparators. Therefore, subsequent treatments are only included following first-line treatment.

Table 66: Subsequent therapies after treatment discontinuation from first-line treatment

	Pralsetinib	Pembro + pemetrexed + chemo	Pembro mono	Treatment duration (months)
Patients who received a subsequent treatment	**69.2%**	**62.8%**	**60.6%**	**--**
Docetaxel	1.5%	23.3%	0.7%	4.1 (77)
Docetaxel + nintedanib	1.5%	18.6%	0.7%	4.1 (77)
Platinum-based chemotherapy without pemetrexed maintenance	35.9%	20.9%	22.0%	3.5 (78)
Platinum-based chemotherapy	25.6%	0.0%	37.1%	3.5 (78)

with pemetrexed maintenance				
Atezolizumab monotherapy	1.5%	0.0%	0.0%	2.8 (77)
Nivolumab monotherapy	1.5%	0.0%	0.0%	2.3 (101)
Pembrolizumab monotherapy	1.5%	0.0%	0.0%	3.9 (104)
Patients who received best supportive care	**30.8%**	**37.2%**	**39.4%**	**--**
Total (all patients)	**100%**	**100%**	**100%**	**--**

Note: subsequent treatment duration for docetaxel + nintedanib was assumed to be equivalent to docetaxel monotherapy

B.3.5.4.2 Subsequent treatment acquisition costs

Drug acquisition costs for the subsequent treatments included in the economic model are summarised in Table 67. For medicines available to the NHS as generic medicines, prices are taken from eMIT, which reports the average price paid by the NHS for a generic medicine for the last period (113). The PAS price was used for atezolizumab including a discount of [redacted]. For other medicines only available to the NHS as proprietary medicines, prices are taken as the list price stated in the BNF (114).

Table 67: Subsequent treatment acquisition costs

Regimen	Drug	Pack size	Price per pack (£)	Cost per treatment cycle	Source
Docetaxel	Docetaxel	1 x 160mg	17.95	21.34	eMIT
Docetaxel + nintedanib	Docetaxel	1 x 160mg	17.95	21.34	eMIT
	Nintedanib	120 x 100mg	2,151.10	2,078.54	BNF
Platinum-based chemotherapy without pemetrexed	Cisplatin	1 x 100mg	8.73	4.43	eMIT
	Carboplatin	1 x 450mg	13.76	31.02	eMIT
Platinum-based chemotherapy with pemetrexed	Cisplatin	1 x 100mg	8.73	4.43	eMIT
	Carboplatin	1 x 450mg	13.76	31.02	eMIT
	Pemetrexed	1 x 100mg	160.00	2,029.17	BNF
Atezolizumab monotherapy	Atezolizumab (with PAS)	1 x 1200mg	[redacted]	[redacted]	--
Nivolumab monotherapy	Nivolumab	1 x 240mg	2,633.00	5,724.42	BNF

Pembrolizumab monotherapy	Pembrolizumab	1x 100mg	2,630.00	7,623.87	BNF

BNF, British National Formulary; eMIT, electronic market information tool

B.3.5.4.3 Subsequent treatment administration costs

Table 68 provides the administration costs assumed for the intervention and comparators.

Table 68: Subsequent treatment administration costs

Regimen	Drug	Type of admin.	Cost per first admin. (£)	Cost per subsequent admin. (£)	Source
Docetaxel	Docetaxel	IV	241.06	241.06	NHS ref. SB12Z
Docetaxel + nintedanib	Docetaxel	IV	241.06	241.06	NHS ref. SB12Z
	Nintedanib	Oral	195.00	15.00	NHS SB11Z; TA643 12 mins pharmacist time
Platinum-based chemotherapy without pemetrexed	Cisplatin	IV	370.68	332.13	NHS ref. SB14Z, SB15Z
	Carboplatin				
Platinum-based chemotherapy with pemetrexed	Cisplatin	IV	370.68	332.13	NHS ref. SB14Z, SB15Z
	Carboplatin				
	Pemetrexed				
Atezolizumab monotherapy	Atezolizumab	IV	241.06	241.06	NHS ref. SB12Z
Nivolumab monotherapy	Nivolumab	IV	241.06	241.06	NHS ref. SB12Z
Pembrolizumab monotherapy	Pembrolizumab	IV	241.06	241.06	NHS ref. SB12Z

NHS, National Health Service

B.3.5.4.3 Subsequent treatment total costs

Table 65 provides the total subsequent treatment costs for each first-line treatment arm. Total costs were calculated for each treatment arm by multiplying the proportion of patients receiving each subsequent treatment, the monthly acquisition cost of each subsequent treatment, the

monthly administration cost of each subsequent treatment and the duration on treatment of each subsequent treatment.

Table 69: Total subsequent treatment costs per treatment arm

Line	Regimen	Total subsequent treatment costs (£)
First-line	Pralsetinib	[redacted]
	Pembrolizumab + pemetrexed + chemotherapy	2,649
	Pembrolizumab monotherapy	3,789

B.3.5.5 Miscellaneous unit costs and resource use

RET fusion-positive patients are identified from wild-type NSCLC patients via genomic testing. Genomic testing costs should be applied in the pralsetinib treatment arms of the untreated and pre-treated cost-effectiveness models to the extent that the potential introduction of pralsetinib as a result of this appraisal increases genomic testing compared to the counterfactual scenario.

After consultation with a clinical expert, it is estimated that the current proportion of advanced NSCLC patients who receive genetic testing to identify the *RET* fusion mutation in 2021 is approximately 30%. The establishment of genomic testing for advanced NSCLC patients is thought to be imminent. The Department of Health and NHSE&I have outlined their NHS Long Term Plan where they have committed to offer whole genome sequencing routinely (500,000 whole genomes) by 2023-24 (48, 96). This will cover *RET* fusion testing in the patient population relevant to this submission. Further, as per the Department of Health's 2021 to 2022 Implementation Plan, a commitment has been made to progress towards this aim in the short term which will coincide with the potential launch of pralsetinib following this appraisal in 2022.

Therefore, it is evident that genomic testing will be implemented for advanced NSCLC patients in the short-term future regardless of the outcome of this appraisal. In the long-run, the impact of the introduction of pralsetinib in this indication will have a negligible impact on genomic testing costs. Therefore, testing costs have not been included in the base case analysis for either untreated or pre-treated analyses.

A scenario analysis has been included to explore the potential impact of testing costs on results where patients receiving pralsetinib are assumed to incur a proportion of genomic testing costs representing the potential increase to genomic testing per patient due to pralsetinib in this indication. For this scenario analysis this proportion is arbitrarily assumed to be 10%.

To estimate the cost of RET fusion testing, an identical method to TA643 was applied (100). Testing was costed in line with the most pragmatic strategy used by UK clinical experts; using the IHC test followed by the confirmatory FISH test. The cost of testing to identify a *RET* fusion patient includes costs for testing patients who test both positive and negative for the *RET* fusion mutation. *RET* fusions have been identified in 1-2% (assumed 1.5%) of NSCLC patients (20-22). The specificity of IHC testing is assumed to be 62.5% (123). As FISH for *RET* testing is the reference test in the diagnostic accuracy, a perfect diagnostics accuracy of FISH *RET* testing was assumed. In line with TA643, the cost of IHC testing was estimated by applying the cost of IHC (£50) to all non-squamous NSCLC patients who would be tested upfront. The cost of confirmatory FISH tests (£120) is then applied to the 1.5% of patients that are expected to be *RET* fusion-positive where 37.5% (100%-62.5%) are expected to receive a false negative result. The total cost of *RET* fusion-positive cost testing per patient was estimated to be of £6,453. Therefore, the total cost attributed to pralsetinib was assumed to be £645. Costs are outlined in Table 70.

Table 70: *RET* fusion testing costs

Test	Cost	Source
IHC	£50	(100)
FISH	£120 IHC: (1.5%+37.5%)=39% Cost of FISH testing £120 * 39% = £46.80	
Total cost of testing	£50 + £46.80 = £96.80	
Total cost per *RET* fusion-positive patient	£96.80/1.5%=£6,453	
Total cost per *RET* fusion-positive patient attributed to pralsetinib	£6,453 * 10% = £645	

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

B.3.6.1 Summary of base-case analysis inputs

A table summarising the full list of variables applied in the economic model is presented in Table 71.

Table 71: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission

Time horizon	25 years	Fixed	B.3.2.2
Model cycle length	Month	Fixed	B.3.2.2
Discount rate – costs/efficacy	3.5%	Fixed	B.3.2.2
Age (untreated)	63.0 years	se= 0.825 (normal)	B.2.3.3
Age (pre-treated)	59.5 years	se= 0.825 (normal)	B.2.3.3
Proportion male (untreated)	52.0%	Beta	B.2.3.3
Proportion male (pre-treated)	45.6%	Beta	B.2.3.3
BSA (untreated)	1.75 m^2	se= 0.017 (normal)	--
BSA (pre-treated)	1.75 m^2	se= 0.017 (normal)	--
OS (pralsetinib untreated)	Weibull curve	Multivariate normal	B.3.3.2
PFS (pralsetinib untreated)	Exponential curve	Multivariate normal	B.3.3.2
TTD (pralsetinib untreated)	Exponential curve	Multivariate normal	B.3.3.2
OS (pralsetinib pre-treated)	Exponential curve	Multivariate normal	B.3.3.3
PFS (pralsetinib pre-treated)	Exponential curve	Multivariate normal	B.3.3.3
TTD (pralsetinib pre-treated)	Exponential curve	Multivariate normal	B.3.3.3
Indirect treatment comparison hazard ratios: OS pem + chemo	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: PFS pem + chemo	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: TTD pem + chemo	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: OS pem mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: PFS pem mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: TTD pem mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: OS doce mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: PFS doce mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9

Indirect treatment comparison hazard ratios: TTD doce mono	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: OS doce + nin	[redacted]	95% CI [redacted](log-normal)	B.2.9
Indirect treatment comparison hazard ratios: PFS doce + nin	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: TTD doce + nin	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: OS PBC +/- P	[redacted]	95% CI 0.[redacted](log-normal)	B.2.9
Indirect treatment comparison hazard ratios: PFS PBC +/- P	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Indirect treatment comparison hazard ratios: TTD PBC +/- P	[redacted]	95% CI [redacted] (log-normal)	B.2.9
Adverse event rates	Many	se=10% (beta)	B.3.3.5
Pralsetinib acquisition costs- 120 x 100mg (PAS)	[redacted]	Fixed	B.3.5.1
Pembrolizumab acquisition costs - 1 x 100mg	2,630.00	Fixed	B.3.5.1
Pemetrexed acquisition costs - 1 x 100mg	160	Fixed	B.3.5.1
Cisplatin acquisition costs - 1 x 100mg	8.73	Fixed	B.3.5.1
Carboplatin acquisition costs - 1 x 450mg	13.76	Fixed	B.3.5.1
Docetaxel acquisition costs - 1 x 160mg	17.95	Fixed	B.3.5.1
Nintedanib acquisition costs - 120 x 100mg	2,151.10	Fixed	B.3.5.1
Oral medication- first administration cost	195.00	Fixed	B.3.5.1
Oral medication- subsequent administration cost	15.00	Fixed	B.3.5.1
Complex chemotherapy IV- first administration cost	370.68	Fixed	B.3.5.1
Complex chemotherapy IV- subsequent administration cost	332.13	Fixed	B.3.5.1
Simple chemotherapy IV administration cost	241.06	Fixed	B.3.5.1

PF supportive care costs	Many	se=10% (normal)	B.3.5.2
PD supportive care costs	Many	se=10% (normal)	B.3.5.2
Terminal care costs	Many	se=10% (normal)	B.3.5.2
Adverse event costs	Many	se=10% (normal)	B.3.5.3
Subsequent treatment duration	Many	se=10% (normal)	B.3.5.4
PF health state utility value (untreated)	0.794	95% CI 0.780, 0.810 (beta)	B.3.4.3
PD health state utility value (untreated)	0.678	95% CI 0.542, 0.814 (beta)	B.3.4.3
PF health state utility value (pre-treated)	0.713	95% CI 0.712, 0.715 (beta)	B.3.4.3
PD health state utility value (pre-treated)	0.628	se=10% (beta)	B.3.4.3
Adverse event disutility	Many	se=10% (normal)	B.3.4.4
Adverse event disutility duration	Many	se=10% (normal)	B.3.4.4

BSA, body surface area; CI, confidence interval; IV, intravenous; OS, overall survival; PAS, patient access scheme; PBC +/- P, platinum based chemotherapy +/- pemetrexed; PD, progressed disease; PF, progression-free; PFS, progression-free survival; SE, standard error; TTD, time-to-discontinuation

B.3.6.2 Assumptions

A table summarising the key assumptions in the economic model is presented in Table 72.

Table 72: Key assumptions used in the economic model

Area	Assumption	Justification
Time horizon	25 years	Based on ARROW data, the average age of patients at the start of the model is 63.0 years in untreated and 59.5 years in pre-treated. The 25 year model time horizon is expected to be long enough to reflect difference in costs and outcomes between treatment arms, as recommended in the NICE reference case (124)
Extrapolation of pralsetinib PFS, OS and TTD	Best fit according to combined data on AIC / BIC statistics, visual fit to observed data and long-term clinical plausibility. Long term extrapolations were validated by UK clinical experts	As recommended in the NICE reference case (124)
Extrapolation of comparator OS, PFS and TTD	Proportional hazards was assumed between pralsetinib and comparators across the model time horizon	Given an indirect treatment comparison was used, proportional hazards was assumed between pralsetinib and all comparators across all endpoints. Distributions consistent with the proportional hazards assumption were selected to model OS, PFS and TTD. The directional impact of any bias on cost-effectiveness results

		that would occur if the proportional hazards assumption were to be violated is unknown.
Indirect treatment comparison: *RET* fusion-positive vs. WT advanced NSCLC	Adjustment for baseline characteristics accounts for clinical outcomes difference between *RET* fusion-positive and WT advanced NSCLC patients. Outside of this baseline characteristic adjustment, *RET* fusion status is not assumed to be a prognostic factor for clinical outcomes in advanced NSCLC	There is a paucity of available evidence for clinical outcomes in RET fusion-positive advanced NSCLC patients. The upcoming chart review (Section B.2.9.3) may provide a *RET* fusion-positive comparison to inform the current submission at a later date. In the absence of suitable data, comparator patient populations were adjusted based on baseline characteristics in order to represent a *RET* fusion-positive patient population. There is also a paucity of evidence outlining the degree to which, after suitably adjusting for baseline characteristics, *RET* fusion status is a prognostic factor in clinical outcomes (2). Differing assumptions for hazard ratios on treatment effect were explored in the sensitivity analysis.
Indirect treatment comparison: real world evidence vs. clinical trial	Real world evidence from Flatiron Health dataset is suitable to compare to clinical trial data to inform decision making	Data were adjusted on baseline characteristics including age and ECOG PS to adjust for potential differences in patient populations. Differing assumptions for hazard ratios on treatment effect were explored in the sensitivity analysis.
Indirect treatment comparison: TTD	In the absence of TTD data in the published literature, the HR on PFS was used as a proxy for the HR on TTD for docetaxel monotherapy and docetaxel + nintedanib	PFS is a commonly used proxy for TTD in NICE oncology appraisals in the absence of published TTD data. It should be noted that in for treatments in the Flatiron Health dataset where both PFS and TTD are available, HRs are comparable. Sensitivity analysis was conducted to explore the impact of using PFS as a proxy for TTD for all treatments. The directional impact of any bias on cost-effectiveness results is unknown.
Indirect treatment comparison: docetaxel + nintedanib	HR for PFS/TTD for docetaxel + nintedanib is equivalent to docetaxel monotherapy	It is not considered clinically plausible that HRs for docetaxel + nintedanib would be less docetaxel monotherapy as this implies a negative treatment effect of the addition of nintedanib to docetaxel. As the docetaxel monotherapy propensity scoring indirect treatment comparison was a more robust analysis than the naïve comparison used for docetaxel + nintedanib, this was used to correct this clinical implausibility for PFS and TTD. By assuming equal efficacy, it is possible outcomes in the docetaxel + nintedanib treatment arm are underestimated. However, clinical experts in the advisory board estimated the additional benefit on survival outcomes from the addition of nintedanib to be negligible.

Indirect treatment comparison: impact of PD-L1 status on outcomes	PD-L1 status is assumed not to be a prognostic factor for clinical outcomes for patients receiving pralsetinib	Pembrolizumab monotherapy as a first-line treatment and platinum-based chemotherapy +/- pemetrexed as a second-line treatment are only available to patients in the PD-L1-positive NICE treatment pathway. Insufficient PD-L1 data was collected in ARROW to inform a PD-L1-positive subgroup. The indirect treatment comparison compares pralsetinib patients (regardless of PD-L1 status) with PD-L1-positive patients in the comparator arm. There is assumed to be no bias on overall results if PD-L1 status is not a prognostic factor for clinical outcomes for patients receiving pralsetinib. Pralsetinib is a *RET* inhibitor and therefore PD-L1 status is unlikely to have any impact on survival. This assumption was validated in an advisory board with clinical experts.
Indirect treatment comparison: Stopping rule for pembrolizumab	It is assumed the stopping rule for pembrolizumab has no impact on survival	In the UK, clinical practice is that patients receiving pembrolizumab have a 2-year stopping rule. Patients in the US-based Flatiron Health dataset are not subjected to the same stopping rule. It is plausible that patients in the Flatiron database who continue on treatment past 2 years will have additional survival benefit compared to the UK where patients receive pembrolizumab up until a 2-year stopping rule. If this is the case then this will bias the treatment effect and cost-effectiveness results against pralsetinib.
Proportion of platinum-based chemotherapy +/- pemetrexed patients on pemetrexed	Proportion of patients assumed to receive pemetrexed is 62.8%	This assumption was made to align with UK practice following clinical expert feedback. This is a conservative assumption as the study used to inform clinical efficacy for the comparator assumed 100% of patients received pemetrexed. Given there is a survival benefit associated with pemetrexed, account for the clinical benefit and only a proportion of costs will bias cost-effectiveness results against pralsetinib
Supportive care and end-of-life costs	Supportive care costs are identical between *RET* fusion-positive and ROS1-positive advanced NSCLC patients	This assumption was validated with clinical experts at an advisory board.
Supportive care costs	Supportive care costs are identical between treatment arms regardless of CNS	Pralsetinib penetrates the blood–brain barrier and is efficacious in brain metastases: an intracranial ORR rate of [redacted] was observed in ten patients with measurable CNS metastases (Table 19). Therefore, pralsetinib may reduce PD supportive care costs in CNS patients compared to comparators. However, given ARROW was a single arm trial, it was not possible estimate the rate of reduction of CNS in patients in pralsetinib

		arms compared to comparators and therefore include the potential cost savings in the economic model.
Health state utilities	HRQoL in *RET* fusion-positive population assumed equivalent to EGFR and WT advanced NSCLC in previous NICE submissions	An SLR was undertaken to identify health state utility values in *RET* fusion-positive patients and found a lack of suitable evidence. This assumption was made in the wake of this evidence gap. This is an assumption that has been used in previous NICE appraisals in advanced NSCLC (71, 100). A variety of different approaches were explored in scenario analysis. The directional impact of any bias on cost-effectiveness results from this assumption is unknown.

AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D, EuroQol- 5 Dimension; HR, hazard ratio; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD-L1 programmed death-ligand 1; PFS, progression-free survival; TTD, time to treatment discontinuation; WT wild type

B.3.7 Base-case results

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

The results of the economic model base-case for the untreated analysis (with PAS for pralsetinib) are presented in Table 73. Patients in the pralsetinib arm had a mean OS of [redacted] and attained [redacted] QALYs at a total cost of [redacted].

In comparison to the primary untreated comparator of pembrolizumab + pemetrexed + chemotherapy, pralsetinib provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained.

In comparison to pembrolizumab monotherapy, pralsetinib provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained.

However, pembrolizumab and pemetrexed are subject to a confidential PAS which is not accounted for here, thus results should be interpreted with caution.

The clinical outcomes and disaggregated base-case cost-effectiveness results are presented in Appendix J. Results with the pralsetinib list price are included in Appendix J.

Table 73: Base-case untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 74 demonstrates base case results for pralsetinib against pembrolizumab + pemetrexed + chemotherapy whilst arbitrarily varying the PAS for pembrolizumab and pemetrexed from 0-100%.

Table 74: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab and pemetrexed PAS: ICER (£/ QALY) pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy

	Pemetrexed PAS										
Pembrolizumab PAS	**0%**	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 75 demonstrates base case results for pralsetinib against pembrolizumab monotherapy whilst arbitrarily varying the PAS for pembrolizumab from 0-100%.

Table 75: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab PAS

Pembrolizumab PAS	ICER (£/ QALY) pralsetinib vs. pembrolizumab monotherapy
0%	[redacted]
10%	[redacted]
20%	[redacted]
30%	[redacted]
40%	[redacted]
50%	[redacted]
60%	[redacted]
70%	[redacted]
80%	[redacted]
90%	[redacted]
100%	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.7.2 Base-case pre-treated incremental cost-effectiveness analysis results

The results of the economic model base-case pre-treated analysis (with PAS for pralsetinib) are presented in Table 76. Patients in the pralsetinib arm had a mean OS of [redacted] and attained [redacted] QALYs at a total cost of [redacted].

In comparison to the primary pre-treated comparator docetaxel monotherapy, pralsetinib provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained.

In comparison to docetaxel + nintedanib, pralsetinib provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained.

In comparison to platinum-based chemotherapy +/- pemetrexed, pralsetinib provides an incremental LYG of [redacted] and an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained.

However, nintedanib and pemetrexed are subject to a confidential PAS which is not accounted for here, thus results should be interpreted with caution.

The clinical outcomes and disaggregated base-case cost-effectiveness results are presented in Appendix J. Results with the pralsetinib list price are included in Appendix J.

Table 76: Base-case pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.8.1 Probabilistic sensitivity analysis

B.3.8.1.1 Untreated

A probabilistic sensitivity analysis (PSA) was undertaken to explore the uncertainty of all model parameters and their associated impact on untreated cost-effectiveness results. A Monte-Carlo simulation was conducted using 5,000 iterations to ensure convergence. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section B.3.6. The results of the untreated PSA (with PAS for pralsetinib) are presented in Table 77.

Table 77: PSA untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 60-Figure 61 display the cost-effectiveness plane of pralsetinib (with PAS for pralsetinib) and untreated comparators based on 5,000 iterations. Figure 62 displays the associated cost-effectiveness acceptability curve.

Figure 60: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab + pemetrexed + chemotherapy

[redacted]

PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 61: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 62: Untreated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.8.1.2 Pre-treated

A PSA was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. A Monte-Carlo simulation was conducted using 5,000 iterations to ensure convergence. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section B.3.6. The results of the pre-treated PSA (with PAS for pralsetinib) are presented in Table 78.

Table 78: PSA pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 63 displays the cost-effectiveness plane of pralsetinib (with PAS for pralsetinib) and pre-treated comparators based on 5,000 iterations. Figure 66 displays the associated cost-effectiveness acceptability curve.

Figure 63: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 64: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel + nintedanib

PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 65: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and platinum-based chemotherapy +/- pemetrexed

PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 66: Pre-treated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.8.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis (DSA) was performed to investigate key drivers of the base-case results. Each input parameter was varied to its respective upper or lower bound and the deterministic results for the model recorded. The base-case parameter values were varied across their 95% CI where possible. In the absence of 95% CIs, parameters were arbitrarily varied +/- 20%. Tornado plots show the six parameters with the largest impact on ICER.

B.3.8.2.1 Untreated

The parameter values used in the DSA for pralsetinib vs. the primary comparator pembrolizumab + pemetrexed + chemotherapy in the untreated analysis and their respective impact on cost-effectiveness results are displayed in Table 79. The associated tornado diagram is presented in Figure 67. The DSA highlighted that the hazard ratios on OS and TTD had the greatest impact on the cost-effectiveness results.

Table 79: Untreated DSA for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per first admin.- pemb + pem + chemo	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%

Cost per subsequent admin.- pemb + pem + chemo	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.794	0.780	[redacted]	0.807	[redacted]	95% CI
PD health state utility value	0.678	0.542	[redacted]	0.814	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Figure 67: Untreated tornado plot for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

[redacted]

PAS, patient access scheme

The parameter values used in the DSA for pralsetinib vs. pembrolizumab monotherapy in the untreated analysis and their respective impact on cost-effectiveness results are displayed in Table 80. The associated tornado diagram is presented in Figure 68. The DSA highlighted that hazard ratios for TTD and OS had the greatest impact on the cost-effectiveness results.

Table 80: Untreated DSA for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- pem mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.794	0.780	[redacted]	0.807	[redacted]	95% CI
PD health state utility value	0.678	0.542	[redacted]	0.814	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Figure 68: Untreated tornado plot for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

[redacted]

PAS, patient access scheme

B.3.8.2.2 Pre-treated

The parameter values used in the DSA for pralsetinib vs. the primary comparator docetaxel monotherapy and their respective impact on cost-effectiveness results are displayed in Table 81. The associated tornado diagram is presented in Figure 69. The DSA highlighted that the hazard ratio for OS and the PD health state utility had the greatest impact on the cost-effectiveness results.

Table 81: Pre-treated DSA for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Figure 69: Pre-treated tornado plot for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)

PAS, patient access scheme

The parameter values used in the DSA for pralsetinib vs. docetaxel + nintedanib and their respective impact on cost-effectiveness results are displayed in Table 82. The associated tornado diagram is presented in Figure 70. The DSA highlighted that the hazard ratios on OS and the PD health state utility value had the greatest impact on the cost-effectiveness results.

Table 82: Pre-treated DSA for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib and doce mono	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib and doce mono	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce + nin	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Figure 70: Pre-treated tornado plot for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

PAS, patient access scheme

The parameter values used in the DSA for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed and their respective impact on cost-effectiveness results are displayed in Table 83. The associated tornado diagram is presented in Figure 71. The DSA highlighted that hazard ratio on OS and the PD health state utility value had the greatest impact on the cost-effectiveness results.

Table 83: Pre-treated DSA for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per first admin.- PBC +/- pem	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- PBC +/- pem	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%

Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Figure 71: Pre-treated tornado plot for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

[redacted]

PAS, patient access scheme

B.3.8.3 Scenario analysis

Scenario analysis was conducted to assess uncertainty around structural assumptions of the model. The list of scenarios explored in the untreated and pre-treated analyses and their impact on cost-effectiveness results are displayed in Table 84.

Table 84: Untreated and pre-treated scenario analysis

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY) pral vs.		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25-years	5-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – costs and QALYs	3.50%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Half cycle correction	Enabled	Disabled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated OS curve selection for pralsetinib	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated OS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (adjusted IPTW)	As per Flatiron analysis adjusted using matching as per Flatiron technical report (79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming no adjustment for metastases)	As per Flatiron analysis assuming adjustment for metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming only ECOG PS 0-1 in eligibility)	As per Flatiron analysis (no ECOG PS restrictions in eligibility criteria)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case	As per naïve comparison (Section B.2.9.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib HRs for OS, PFS, TTD	Assumed equal to docetaxel mono	As per naïve comparison	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method for modelling treatment duration	TTD as per ARROW	Assumed equal to PFS as per ARROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule for pembrolizumab	2-year stopping rule	No stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients in PBC +/- pemetrexed arm receiving pemetrexed	62.8% as per UK clinical practice	100% as per clinical efficacy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion testing costs	Not included	Included as per Section B.3.5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated health state utility values	PF: 0.794 PD: 0.678	PF: 0.784 PD: 0.725	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.794 PD: 0.678	PF: 0.780 PD: 0.660	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated health state utility values	PF: 0.713 PD: 0.628	PF: 0.853 PD: 0.659	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.713 PD: 0.628	PF: 0.672 PD: 0.653	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

B.3.8.4 Summary of sensitivity analyses results

PSA, DSA and scenario analysis have been conducted to investigate the uncertainty around the economic model for the untreated and pre-treated analysis.

In the untreated PSA, pralsetinib demonstrated a cost-effective treatment option against the primary comparator pembrolizumab + pemetrexed + chemotherapy and against the secondary comparator pembrolizumab monotherapy at the £50,000 end-of-life cost-effectiveness threshold. However, pralsetinib is not a cost-effective treatment option against docetaxel monotherapy, docetaxel + nintedanib or platinum-based chemotherapy +/- pemetrexed in the pre-treated population. Nevertheless, as discussed previously, based on the degree of unmet medical need and the potential benefits of earlier targeted treatment, the untreated population is the primary focus for pralsetinib in this appraisal. This position was validated by clinical experts in an advisory board and [redacted] who stated a preference for the usage of pralsetinib in the untreated population. The results of the untreated and pre-treated PSAs closely aligned to deterministic results.

The result of cost-effectiveness to both comparators in the untreated population held across all sensitivity and scenario analyses for both comparators. Across both populations, results were most sensitive to the OS and TTD hazard ratios estimated from the indirect treatment comparison.

B.3.9 Subgroup analysis

A subgroup analysis was not conducted in the economic analysis.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Selection of the appropriate distributions for time-to-event endpoints for pralsetinib was driven by statistical fit to the data, visual fit to the Kaplan-Meier and, importantly, clinical plausibility of the outcomes as per an advisory board with clinical experts (See section B.3.3). Outputs from the indirect treatment comparison (Section B.2.9) were also assessed for clinical plausibility and validated by clinical experts.

The economic model was developed specifically from the UK NHS and PSS perspective. The structure is consistent with previous advanced NSCLC submissions to NICE (71). All costs are sourced from UK published sources. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model is reflective of clinical

practice. This includes, but is not limited to health state inclusion, relevant comparators, resource use, OS, PFS and TTD projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of pressure tests were also conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Relative importance of untreated and pre-treated populations

In order to align with the anticipated licence and the scope, Roche has submitted economic analyses in both untreated and pre-treated populations. However, given the ongoing unmet medical need in this patient population and the potential benefits of earlier targeted treatment Roche views the untreated population as the target patient population for pralsetinib in this appraisal. This position was validated by clinical experts in an advisory board [redacted] who stated a preference for the usage of pralsetinib in the untreated population.

B.3.11.2 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England as:

- The patient population in the economic model is identical to that in ARROW that is comparable with the *RET* fusion-positive NSCLC population expected in UK clinical practice, as per expert clinical advice. ARROW data informed the clinical and safety inputs in the economic model.
- The economic model structure is consistent with other oncology models and previous NICE submissions in *RET* fusion-positive NSCLC.
- The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs, PSSRU and previous NICE submissions. These cost inputs are considered most appropriate to model the cost-effectiveness of pralsetinib.
- All key inputs and assumptions in the economic model were validated by UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

B.3.11.3 Strengths and weaknesses of the evaluation

The key strengths associated with the cost-effectiveness analysis are related to the use of the best available evidence and methods to inform the model given the paucity of data in the *RET* fusion-positive NSCLC disease setting:

- Efficacy and safety data from ARROW were used to model OS, PFS, TTD and adverse events for the pralsetinib treatment arm.
- The long-term efficacy projections from the model were made using methodologies to follow NICE guidance and validated by UK clinical experts to ensure the clinical plausibility of the model (section B.3.10).
- Resource utilisation used in the analysis is derived from previous NICE appraisals relating to advanced NSCLC and clinical expert opinion. Unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from UK published sources and previous NICE appraisals, accounting for the feedback provided by NICE and ERGs in the most recent submissions.
- Relevant comparators for *RET* fusion-positive patients in the current UK treatment pathway were identified in consultation with clinical experts at an advisory board.
- The indirect treatment comparison implemented enabled a comparison between pralsetinib and relevant comparators for UK treatment in RET fusion-positive advanced NSCLC by applying appropriate methodology and making use of all available evidence. Comparator patients were adjusted on baseline characteristics to account for differences in characteristics between *RET* fusion-positive and WT advanced NSCLC patients.
- To account for any potential uncertainty, extensive sensitivity and scenario analyses were conducted in the economic model to inform the uncertainty around the parameters used and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.

Nevertheless, the economic analysis is also associated with limitations:

- To date, there have been a low number of deaths in the ARROW clinical trial in the subgroup relevant to this submission. Therefore, the data remains immature with uncertainty around long-term survival. Conservative extrapolations were made in the economic model to account for this and the approach taken was validated with clinical experts in an advisory board
- Extrapolation of time-to-event endpoints is also subject to uncertainty. This is a common uncertainty in oncology NICE appraisals. Nevertheless, by following a robust and

comprehensive approach for the survival extrapolation, the best efforts have been taken to ensure the methods were statistically sound, clinically plausible, and reflective of real-world clinical practice. Extensive sensitivity and scenario analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario

- ARROW was a single arm study that informed clinical efficacy of pralsetinib in this submission. No RCT data was available for pralsetinib and therefore treatment effectiveness had to be estimated via an indirect treatment comparison
- No *RET* fusion-positive studies that were adequate for decision making were identified to inform the indirect comparison in this appraisal (Section B.2.9.1-3). Therefore an indirect treatment comparison against studies with a WT NSCLC patient population were conducted. In the untreated setting, patient populations were matched to account for differing patient characteristics between the ARROW and Flatiron EDM dataset. There is no evidence for prognostic differences between *RET* and WT patient populations (2, 71). Roche have attempted to address this limitation with the ongoing chart review analysis (Section B.2.9.3) which aims to conduct a comparison against a historical cohort of *RET* fusion-positive patients. Roche hopes to provide this analysis in time for clarification questions
- The indirect treatment comparison that informs the untreated economic analyses was a comparison between trial data and real world evidence. However, baseline characteristics were adjusted to account for any differences in patient characteristics between the patient populations
- The pembrolizumab monotherapy in UK clinical practice represents a PD-L1 (tumor proportion score) ≥50% patient population as per the EMA license. The Flatiron dataset is a real world US based dataset. PD-L1 status is not recorded in the Flatiron dataset. However, the FDA license is PD-L1 (tumor proportion score) ≥1%, therefore, it is likely that majority of patients in the Flatiron database would have PD-L1 status of ≥1%. Pembrolizumab may be more effective in a PD-L1 ≥50% setting compared to PD-L1 ≥1%.
- The indirect treatment comparison that informs the untreated economic analyses uses data from pembrolizumab patients in the US. In the UK, clinical practice is that patients receiving pembrolizumab have a 2-year stopping rule. Patients in the US-based Flatiron Health dataset are not subjected to the same stopping rule. It is plausible that patients in the Flatiron database who continue on treatment past 2 years will have additional survival benefit compared to the UK where patients receive pembrolizumab up until a 2-

year stopping rule. If this is the case then this will bias the treatment effect and cost-effectiveness results against pralsetinib

- HRQoL was not measured in the ARROW clinical trial and therefore health state utilities in the economic model could not be modelled from trial data as per the NICE reference case. However, the economic analyses has used health state utility values from comparable patient populations that have been accepted in previous NICE appraisals
- Pralsetinib penetrates the blood–brain barrier and is efficacious in brain metastases: an intracranial ORR rate of [redacted] was observed in ten patients with measurable CNS metastases. Therefore, pralsetinib may reduce PD supportive care costs in CNS patients compared to comparators. However, given ARROW was a single arm trial, it was not possible estimate the rate of reduction of CNS in patients in pralsetinib arms compared to comparators and therefore include the potential cost savings in the economic model.

Uncertainty in a number of these limitations can be addressed for the untreated analysis with the upcoming AcceleRET-Lung clinical trial (85). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care for first-line treatment of *RET* fusion-positive, advanced NSCLC. Recruitment is expected to be completed in [redacted] with results expected in [redacted].

B.3.11.4 Conclusions

Overall, there is accumulating evidence that the currently recommended treatment options for patients with advanced NSCLC and documented *RET* fusions do not offer the efficacy that has been achieved in patients with NSCLC and other identified oncogenes (such as EGFR and ALK). Existing non-targeted therapy for these patients is associated with significant toxicity and safety risks. To date, no selective *RET*-directed targeted therapies have received NICE approval for the treatment of molecularly defined populations of patients with *RET*-mutant or *RET* fusion–positive solid tumours. Therefore, *RET* fusion–positive NSCLC remains an unmet need that requires new therapeutic options to improve outcomes and generate cost savings, especially in untreated patients given the benefits associated with earlier targeted therapy and the risk of unnecessary potential toxicity associated with standard systemic, non-targeted treatments. Given the degree of unmet medical need together with the preference of UK clinical experts, the untreated population is the primary focus for the current appraisal.

Pralsetinib is a highly selective, potent and efficacious *RET* inhibitor. Data from the ARROW study demonstrate that pralsetinib elicits clinically meaningful and durable responses in advanced *RET* fusion-positive NSCLC in both the untreated population and pre-treated

patients, including those with CNS metastases. In particular, the ARROW study provides evidence that pralsetinib can address the unmet need in the untreated population by providing the option of an efficacious targeted therapy. The benefit of earlier treatment in *RET* fusion-positive NSCLC patients is demonstrated by the greater ORR with pralsetinib in the treatment-naïve group (79.4% [95% CI: 67.9, 88.3]) compared to the pre-treated population (63.5% [95% CI: 55.2, 71.3]).

Moreover, pralsetinib is generally well tolerated and has a safety profile that compares favourably with current standard of care options. The low discontinuation rate and manageable treatment-related AEs in ARROW is supportive of long-term treatment with pralsetinib with the potential for maintenance of quality of life, particularly as it is an orally administered therapy that is more convenient for patients.

As ARROW is a single arm basket trial, an indirect treatment comparison was conducted to estimate treatment effectiveness against the untreated and pre-treated comparators. Given the paucity of evidence available for *RET* fusion-positive patient populations in both the published literature and real world evidence, WT populations were considered and adjusted to reflect a *RET* fusion-positive population (as per ARROW) where possible. ARROW shows a significant improvement in survival for pralsetinib in untreated patients over primary comparator pembrolizumab + pemetrexed + chemotherapy ([redacted]) and secondary comparator pembrolizumab monotherapy ([redacted]). This increase in survival, combined with the manageable safety profile demonstrate that pralsetinib has a favourable benefit/risk profile and addresses the unmet need for this population. In the additional pre-treated analysis, pralsetinib also demonstrates a significant improvement in survival in pre-treated patients over primary comparator docetaxel monotherapy ([redacted]), docetaxel + nintedanib ([redacted]) and platinum-based chemotherapy +/- pemetrexed ([redacted]).

Two economic analyses were conducted to evaluate the cost-effectiveness of pralsetinib in untreated and pre-treated RET fusion-positive advanced NSCLC. Data from the ARROW clinical trial was used to estimate clinical efficacy for pralsetinib. Endpoints were extrapolated over the model time horizon in line with NICE guidance. Treatment effectiveness of pralsetinib against relevant untreated and pre-treated comparators was estimated from the indirect treatment comparison. Pralsetinib meets the NICE end-of-life criteria in both the untreated and pre-treated setting.

In the economic analysis the results demonstrate that pralsetinib represents a cost-effective treatment option in the untreated population, against both the primary comparator

pembrolizumab + pemetrexed + chemotherapy (ICER £[redacted] per QALY) and the secondary comparator pembrolizumab monotherapy at the £50,000 end-of-life cost-effectiveness threshold (ICER £[redacted] per QALY). Pembrolizumab and pemetrexed are subject to a confidential PAS which is not accounted for, thus results should be interpreted with caution. However, results demonstrate that pralsetinib is cost-effective at the £50,000 end-of-life cost-effectiveness threshold up until a [redacted] PAS for pembrolizumab in the comparison to pembrolizumab + pemetrexed + chemotherapy and a [redacted] PAS in the comparison to pembrolizumab monotherapy.

The base case result of cost-effectiveness to both comparators in the untreated population held across all sensitivity and scenario analyses. Measures have been taken to address the uncertainty in the analysis and validate all assumptions made which enables the results to be appropriate for decision-making.

In the pre-treated setting, pralsetinib offers an incremental QALY gain at an increased cost to the healthcare system compared to comparators. At the £50,000 end-of-life cost-effectiveness threshold, pralsetinib does not demonstrate a cost-effective option against either of the three comparators (ICER vs docetaxel monotherapy: [redacted]; ICER vs docetaxel + nintedanib: [redacted]; ICER vs platinum-based chemotherapy +/- pemetrexed: [redacted]).

In summary, pralsetinib can provide the only targeted treatment option for this patients in *RET*-positive NSCLC. Pralsetinib demonstrated a statistically significant benefit in survival compared to standard of care in the untreated and pre-treated settings. Pralsetinib provides a cost-effective targetted treatment option for untreated patients with RET fusion-positive NSCLC, and pralsetinib will spare this population from the poor outcomes and unnecessary potential toxicity associated with standard non-targeted therapies, whilst also freeing up capacity in the healthcare system due to the oral administration. Finally. pralsetinib is estimated to have a minimal budget impact across the untreated and pre-treated settings.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

Clarification questions response

November 2021

File name	Version	Contains confidential information	Date
ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CQ Responses_ACIC	2.0	Yes	11 November 2021

Section A: Literature searches

A1. Please provide full details of the searches of conference proceedings referred to in Appendices D.1, G.2, H.2, I.2 and L.2, including the specific resources searched, the search strategies or search terms used, date searched, and results.

Details of the resources, search terms, dates and results of searches of conference proceedings are provided below.

Table 1: Clinical SLR: hand searching methodology and findings for conference proceedings

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ASCO Annual Meeting 2019	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	31	0
			"Non-small cell lung cancer" AND "ret"	31	0
			"NSCLC" AND "ret"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	44	0
			"Non-small cell lung cancer" AND "ret"	44	0
			"NSCLC" AND "ret"	42	0
ELCC 2020	21/10/2020	Cancelled	NA	NA	NA
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	RET	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149): https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F	RET	6	0
52nd ESHG Conference 2019	22/10/2020	https://www.nature.com/collections/afhijbfgib Searched oral presentations PDF using CTRL + F	RET(space)	3	0
			RET+	0	0
			RET-	0	0
			Lung	22	0
51st ESHG Conference 2018	22/10/2020	https://www.nature.com/collections/dcbjhfbdad/ Searched oral presentations PDF using CTRL + F	RET(space)	4	0
			RET+	0	0
			RET-	0	0
			lung	9	0

50th ESHG Conference 2017	22/10/2020	https://www.nature.com/collections/ygctjrwfhb	RET(space)	7	0
			RET+	0	0
			RET-	0	0
			Lung	4	0
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	NA	NA	NA
ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	RET	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	RET	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ISPOR US 2020, Orlando	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	2	0
			“Non-small cell lung cancer” AND “ret”	2	0
			“NSCLC” AND “ret”	2	0
ISPOR US 2019, New Orleans	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR US 2018, Baltimore	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2019, Copenhagen	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2018, Barcelona	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0

		resources/presentations-database/search	"NSCLC" AND "ret"	0	0
ISPOR Europe 2017, Glasgow	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
HTAi 2019, Cologne	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2019-cologne/abstract-book/ searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	50	0
HTAi 2018, Vancouver	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2018-vancouver/abstract-book/ searched using CTRL + F	RET(space)	11	0
			RET+	0	0
			RET-	0	0
			Lung cancer	15	0
HTAi 2017, Rome	22/10/2020	Abstract booklet: https://htai.org/wp-content/uploads/2018/09/AM17_Rome_Abstractbook_Final-1.pdf searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	31	0
NCRI Cancer Conference 2019	22/10/2020	https://abstracts.ncri.org.uk/year_published/2019/ Searched using search online search feature	Non small cell lung cancer	18	0
			Non-small cell lung cancer	17	0
			NSCLC	13	0
NCRI Cancer Conference 2018	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	28	0
			Non-small cell lung cancer	25	0
			NSCLC	24	0
NCRI Cancer Conference 2017	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	19	0
			Non-small cell lung cancer	17	0
			NSCLC	20	0
SMDM 17th Biennial European Conference 2018	22/10/2020	Scientific program: https://smdm.confex.com/smdm/17bec/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=NSCLC	"Non small cell lung cancer"	2	0
			"Non-small cell lung cancer"	2	0
			"NSCLC"	2	0
SMDM 41st North American Meeting 2019	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2019/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	4	0
			"Non-small cell lung cancer"	4	0
			"NSCLC"	3	0
SMDM 40th North American Meeting 2018	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2018/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	3	0
			"Non-small cell lung cancer"	3	0
			"NSCLC"	3	0
	22/10/2020	Scientific program search: https://smdm.confex.com/smd	"Non small cell lung cancer"	1	0

SMDM 39th North American Meeting 2017		m/2017/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non-small cell lung cancer"	1	0
			"NSCLC"	0	0
USCAP Annual Meeting 2020	22/10/2020	Abstracts from USCAP 2020: Pulmonary, Mediastinum, Pleura, and Peritoneum Pathology (1869-1980): https://www.nature.com/articles/s41379-020-0485-4 Searched PDF using CTRL + F	RET(space)	12	0
			RET+	0	0
			RET-	0	0
USCAP Annual Meeting 2019	22/10/2020	Abstracts from USCAP 2019: Pulmonary Pathology (1803-1896), searched PDF using CTRL + F: https://www.nature.com/articles/s41379-019-0244-6	RET(space)	18	0
			RET+	0	0
			RET-	1	0
USCAP Annual Meeting 2018	22/10/2020	USCAP 2018 Abstracts: Pulmonary Pathology (2011–2128), searched PDF using CTRL + F: https://www.nature.com/articles/modpathol201822	RET(space)	9	0
			RET+	0	0
			RET-	0	0

Table 2: Cost-effectiveness SLR: hand searching methodology and findings for conference proceedings

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ASCO Annual Meeting 2019	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	31	0
			"Non-small cell lung cancer" AND "ret"	31	0
			"NSCLC" AND "ret"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	44	0
			"Non-small cell lung cancer" AND "ret"	44	0
			"NSCLC" AND "ret"	42	0
ELCC 2020	21/10/2020	Cancelled	NA	NA	NA
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	RET	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149):	RET	6	0

Source	Date	Search details	Search terms	No. hits	Downloaded
		https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F			
52nd ESHG Conference 2019	22/10/2020	https://www.nature.com/collections/afhijbfgib Searched oral presentations PDF using CTRL + F	RET(space)	3	0
			RET+	0	0
			RET-	0	0
			Lung	22	0
51st ESHG Conference 2018	22/10/2020	https://www.nature.com/collections/dcbjhfbdad/ Searched oral presentations PDF using CTRL + F	RET(space)	4	0
			RET+	0	0
			RET-	0	0
			lung	9	0
50th ESHG Conference 2017	22/10/2020	https://www.nature.com/collections/ygctjrwfhb	RET(space)	7	0
			RET+	0	0
			RET-	0	0
			Lung	4	0
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	NA	NA	NA
ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	RET	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	RET	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ISPOR US 2020, Orlando	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	2	0
			“Non-small cell lung cancer” AND “ret”	2	0
			“NSCLC” AND “ret”	2	0
ISPOR US 2019, New Orleans	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
	22/10/2020	ISPOR Presentations Database, keyword search	“Non small cell lung cancer” AND “ret”	0	0

Source	Date	Search details	Search terms	No. hits	Downloaded
ISPOR US 2018, Baltimore		filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2019, Copenhagen	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2018, Barcelona	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2017, Glasgow	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
HTAi 2019, Cologne	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2019-cologne/abstract-book/ searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	50	0
HTAi 2018, Vancouver	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2018-vancouver/abstract-book/ searched using CTRL + F	RET(space)	11	0
			RET+	0	0
			RET-	0	0
			Lung cancer	15	0
HTAi 2017, Rome	22/10/2020	Abstract booklet: https://htai.org/wp-content/uploads/2018/09/AM17_Rome_Abstractbook_Final-1.pdf searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	31	0
NCRI Cancer Conference 2019	22/10/2020	https://abstracts.ncri.org.uk/year_published/2019/ Searched using search online search feature	Non small cell lung cancer	18	0
			Non-small cell lung cancer	17	0
			NSCLC	13	0
NCRI Cancer Conference 2018	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	28	0
			Non-small cell lung cancer	25	0
			NSCLC	24	0
NCRI Cancer Conference 2017	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	19	0
			Non-small cell lung cancer	17	0
			NSCLC	20	0
	22/10/2020	Scientific program: https://smdm.confex.com/smd	"Non small cell lung cancer"	2	0

Source	Date	Search details	Search terms	No. hits	Downloaded
SMDM 17th Biennial European Conference 2018		m/17bec/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=NSCLC	"Non-small cell lung cancer"	2	0
			"NSCLC"	2	0
SMDM 41st North American Meeting 2019	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2019/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	4	0
			"Non-small cell lung cancer"	4	0
			"NSCLC"	3	0
SMDM 40th North American Meeting 2018	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2018/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	3	0
			"Non-small cell lung cancer"	3	0
			"NSCLC"	3	0
SMDM 39th North American Meeting 2017	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2017/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	1	0
			"Non-small cell lung cancer"	1	0
			"NSCLC"	0	0
USCAP Annual Meeting 2020	22/10/2020	Abstracts from USCAP 2020: Pulmonary, Mediastinum, Pleura, and Peritoneum Pathology (1869-1980): https://www.nature.com/articles/s41379-020-0485-4 Searched PDF using CTRL + F	RET(space)	12	0
			RET+	0	0
			RET-	0	0
USCAP Annual Meeting 2019	22/10/2020	Abstracts from USCAP 2019: Pulmonary Pathology (1803-1896), searched PDF using CTRL + F: https://www.nature.com/articles/s41379-019-0244-6	RET(space)	18	0
			RET+	0	0
			RET-	1	0
USCAP Annual Meeting 2018	22/10/2020	USCAP 2018 Abstracts: Pulmonary Pathology (2011–2128), searched PDF using CTRL + F: https://www.nature.com/articles/modpathol201822	RET(space)	9	0
			RET+	0	0
			RET-	0	0

Table 3: HSUV SLR: hand searching methodology and findings for conference proceedings

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
	21/10/2020		"Non small cell lung cancer" AND "ret"	31	0

Source	Date	Search details	Search terms	No. hits	Downloaded
ASCO Annual Meeting 2019		ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non-small cell lung cancer" AND "ret"	31	0
			"NSCLC" AND "ret"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	44	0
			"Non-small cell lung cancer" AND "ret"	44	0
			"NSCLC" AND "ret"	42	0
ELCC 2020	21/10/2020	Cancelled	NA	NA	NA
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	RET	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149): https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F	RET	6	0
52nd ESHG Conference 2019	22/10/2020	https://www.nature.com/collections/afhijbfgib Searched oral presentations PDF using CTRL + F	RET(space)	3	0
			RET+	0	0
			RET-	0	0
			Lung	22	0
51st ESHG Conference 2018	22/10/2020	https://www.nature.com/collections/dcbjhfbdad/ Searched oral presentations PDF using CTRL + F	RET(space)	4	0
			RET+	0	0
			RET-	0	0
			lung	9	0
50th ESHG Conference 2017	22/10/2020	https://www.nature.com/collections/ygctjrwfhb	RET(space)	7	0
			RET+	0	0
			RET-	0	0
			Lung	4	0
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	NA	NA	NA
ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	RET	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	RET	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA

Source	Date	Search details	Search terms	No. hits	Downloaded
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ISPOR US 2020, Orlando	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	2	0
			"Non-small cell lung cancer" AND "ret"	2	0
			"NSCLC" AND "ret"	2	0
ISPOR US 2019, New Orleans	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR US 2018, Baltimore	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2019, Copenhagen	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2018, Barcelona	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ISPOR Europe 2017, Glasgow	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
HTAi 2019, Cologne	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2019-cologne/abstract-book/ searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	50	0
HTAi 2018, Vancouver	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2018-vancouver/abstract-book/ searched using CTRL + F	RET(space)	11	0
			RET+	0	0
			RET-	0	0
			Lung cancer	15	0
	22/10/2020	Abstract booklet: https://htai.org/wp-	RET(space)	6	0
			RET+	0	0

Source	Date	Search details	Search terms	No. hits	Downloaded
HTAi 2017, Rome		content/uploads/2018/09/AM17_Rome_Abstractbook_Final-1.pdf searched using CTRL + F	RET-	0	0
			Lung cancer	31	0
NCRI Cancer Conference 2019	22/10/2020	https://abstracts.ncri.org.uk/year_published/2019/ Searched using search online search feature	Non small cell lung cancer	18	0
			Non-small cell lung cancer	17	0
			NSCLC	13	0
NCRI Cancer Conference 2018	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	28	0
			Non-small cell lung cancer	25	0
			NSCLC	24	0
NCRI Cancer Conference 2017	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	19	0
			Non-small cell lung cancer	17	0
			NSCLC	20	0
SMDM 17th Biennial European Conference 2018	22/10/2020	Scientific program: https://smdm.confex.com/smdm/17bec/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=NSCLC	“Non small cell lung cancer”	2	0
			“Non-small cell lung cancer”	2	0
			“NSCLC”	2	0
SMDM 41st North American Meeting 2019	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2019/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	4	0
			“Non-small cell lung cancer”	4	0
			“NSCLC”	3	0
SMDM 40th North American Meeting 2018	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2018/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	3	0
			“Non-small cell lung cancer”	3	0
			“NSCLC”	3	0
SMDM 39th North American Meeting 2017	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2017/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	1	0
			“Non-small cell lung cancer”	1	0
			“NSCLC”	0	0
USCAP Annual Meeting 2020	22/10/2020	Abstracts from USCAP 2020: Pulmonary, Mediastinum, Pleura, and Peritoneum Pathology (1869-1980): https://www.nature.com/articles/s41379-020-0485-4 Searched PDF using CTRL + F	RET(space)	12	0
			RET+	0	0
			RET-	0	0
USCAP Annual Meeting 2019	22/10/2020	Abstracts from USCAP 2019: Pulmonary Pathology (1803-1896), searched PDF using CTRL + F: https://www.nature.com/articles/s41379-019-0244-6	RET(space)	18	0
			RET+	0	0
			RET-	1	0
	22/10/2020		RET(space)	9	0

Source	Date	Search details	Search terms	No. hits	Downloaded
USCAP Annual Meeting 2018		USCAP 2018 Abstracts: Pulmonary Pathology (2011–2128), searched PDF using CTRL + F: https://www.nature.com/articles/modpathol201822	RET+	0	0
			RET-	0	0

Table 4: Costs and resource use SLR: hand searching methodology and findings for conference proceedings

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ASCO Annual Meeting 2019	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	31	0
			"Non-small cell lung cancer" AND "ret"	31	0
			"NSCLC" AND "ret"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	44	0
			"Non-small cell lung cancer" AND "ret"	44	0
			"NSCLC" AND "ret"	42	0
ELCC 2020	21/10/2020	Cancelled	NA	NA	NA
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	RET	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149): https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F	RET	6	0
52nd ESHG Conference 2019	22/10/2020	https://www.nature.com/collections/afhijbfgib Searched oral presentations PDF using CTRL + F	RET(space)	3	0
			RET+	0	0
			RET-	0	0
			Lung	22	0
51st ESHG Conference 2018	22/10/2020	https://www.nature.com/collections/dcbjhfbdad/ Searched oral presentations PDF using CTRL + F	RET(space)	4	0
			RET+	0	0
			RET-	0	0
			lung	9	0
50th ESHG Conference 2017	22/10/2020	https://www.nature.com/collections/ygctjrwfhb	RET(space)	7	0
			RET+	0	0
			RET-	0	0
			Lung	4	0

Source	Date	Search details	Search terms	No. hits	Downloaded
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	NA	NA	NA
ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	RET	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	RET	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ISPOR US 2020, Orlando	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	2	0
			“Non-small cell lung cancer” AND “ret”	2	0
			“NSCLC” AND “ret”	2	0
ISPOR US 2019, New Orleans	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR US 2018, Baltimore	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2019, Copenhagen	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2018, Barcelona	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0

Source	Date	Search details	Search terms	No. hits	Downloaded
ISPOR Europe 2017, Glasgow	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
HTAi 2019, Cologne	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2019-cologne/abstract-book/ searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	50	0
HTAi 2018, Vancouver	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2018-vancouver/abstract-book/ searched using CTRL + F	RET(space)	11	0
			RET+	0	0
			RET-	0	0
			Lung cancer	15	0
HTAi 2017, Rome	22/10/2020	Abstract booklet: https://htai.org/wp-content/uploads/2018/09/AM17_Rome_Abstractbook_Final-1.pdf searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	31	0
NCRI Cancer Conference 2019	22/10/2020	https://abstracts.ncri.org.uk/year_published/2019/ Searched using search online search feature	Non small cell lung cancer	18	0
			Non-small cell lung cancer	17	0
			NSCLC	13	0
NCRI Cancer Conference 2018	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	28	0
			Non-small cell lung cancer	25	0
			NSCLC	24	0
NCRI Cancer Conference 2017	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	19	0
			Non-small cell lung cancer	17	0
			NSCLC	20	0
SMDM 17th Biennial European Conference 2018	22/10/2020	Scientific program: https://smdm.confex.com/smdm/17bec/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=NSCLC	"Non small cell lung cancer"	2	0
			"Non-small cell lung cancer"	2	0
			"NSCLC"	2	0
SMDM 41st North American Meeting 2019	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2019/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	4	0
			"Non-small cell lung cancer"	4	0
			"NSCLC"	3	0
SMDM 40th North American Meeting 2018	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2018/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non small cell lung cancer"	3	0
			"Non-small cell lung cancer"	3	0
			"NSCLC"	3	0
	22/10/2020	Scientific program search: https://smdm.confex.com/smd	"Non small cell lung cancer"	1	0

Source	Date	Search details	Search terms	No. hits	Downloaded
SMDM 39th North American Meeting 2017		m/2017/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	"Non-small cell lung cancer"	1	0
			"NSCLC"	0	0
USCAP Annual Meeting 2020	22/10/2020	Abstracts from USCAP 2020: Pulmonary, Mediastinum, Pleura, and Peritoneum Pathology (1869-1980): https://www.nature.com/articles/s41379-020-0485-4 Searched PDF using CTRL + F	RET(space)	12	0
			RET+	0	0
			RET-	0	0
USCAP Annual Meeting 2019	22/10/2020	Abstracts from USCAP 2019: Pulmonary Pathology (1803-1896), searched PDF using CTRL + F: https://www.nature.com/articles/s41379-019-0244-6	RET(space)	18	0
			RET+	0	0
			RET-	1	0
USCAP Annual Meeting 2018	22/10/2020	USCAP 2018 Abstracts: Pulmonary Pathology (2011–2128), searched PDF using CTRL + F: https://www.nature.com/articles/modpathol201822	RET(space)	9	0
			RET+	0	0
			RET-	0	0

Table 5: WT NSCLC SLR: hand searching methodology and findings for conference proceedings

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer"	0	0
			"NSCLC"	0	0
ASCO Annual Meeting 2019	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer"	31	0
			"NSCLC"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer"	44	0
			"NSCLC"	42	0
ELCC 2020	21/10/2020	Cancelled	NA	NA	NA
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	"Non small cell lung cancer" and "NSCLC"	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149):	"Non small cell lung cancer" and "NSCLC"	6	0

		https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F			
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	NA	NA	NA
ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	"Non small cell lung cancer" and "NSCLC"	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	"Non small cell lung cancer" and "NSCLC"	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	NA	NA	NA

A2. Please provide full details of the searches of health technology assessment organisations referred to in Appendices D.1, G.2, H.2, I.2 and L.2, including the specific resources searched, the search strategies or search terms used, date searched, and results.

Table 6: Clinical SLR: hand searching methodology and findings for HTA organisations

Source	Date	Search details	Search terms	No. hits	Downloaded
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
G-BA	20/10/2020	https://www.g-ba.de/beschluesse/ Searched terms within decision section, filtered for final reports	Non small cell lung cancer AND ret	80	0
HAS	20/10/2020	https://www.has-sante.fr/jcms/fc_2875208/en/search-for-a-guideline-an-assesment All publications by topic, filtered for respiratory	NA	12	0

		tract diseases -> Respiratory tract cancers			
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0
IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on "Guidance" and published "Technology Appraisal Guidance"	Non small cell lung cancer	41	0
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pralsetinib	0	0
			Selpercatinib	0	0
			Pembrolizumab	28	0
			Pemetrexed	9	0
			Atezolizumab	8	0
			Bevacizumab	12	0
			Carboplatin	0	0
			Cisplatin	0	0
			Paclitaxel	7	0
			Docetaxel	9	0
			Gemcitabine	0	0
			Vinorelbine	3	0
			Nintedanib	5	0
			Nivolumab	28	0
SMC	20/10/2020	https://www.scottishmedicines.org.uk/. Searched terms in search bar	Non small cell lung cancer	62	0

Table 7: Cost-effectiveness SLR: hand searching methodology and findings for HTA organisations

Source	Date	Search details	Search terms	No. hits	Downloaded
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
G-BA	20/10/2020	https://www.g-ba.de/beschluesse/ Searched terms within decision section, filtered for final reports	Non small cell lung cancer AND ret	80	0
HAS	20/10/2020	https://www.has-sante.fr/jcms/fc_2875208/en/search-for-a-guideline-an-assesment All publications by	NA	12	0

Source	Date	Search details	Search terms	No. hits	Downloaded
		topic, filtered for respiratory tract diseases -> Respiratory tract cancers			
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0
IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on "Guidance" and published "Technology Appraisal Guidance"	Non small cell lung cancer	41	0
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pralsetinib	0	0
			Selpercatinib	0	0
			Pembrolizumab	28	0
			Pemetrexed	9	0
			Atezolizumab	8	0
			Bevacizumab	12	0
			Carboplatin	0	0
			Cisplatin	0	0
			Paclitaxel	7	0
			Docetaxel	9	0
			Gemcitabine	0	0
			Vinorelbine	3	0
			Nintedanib	5	0
			Nivolumab	28	0
SMC	20/10/2020	https://www.scottishmedicines.org.uk/. Searched terms in search bar	Non small cell lung cancer	62	0

Table 8: HSUV SLR: hand searching methodology and findings for HTA organisations

Source	Date	Search details	Search terms	No. hits	Downloaded
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
G-BA	20/10/2020	https://www.g-ba.de/beschluesse/ Searched terms within decision section, filtered for final reports	Non small cell lung cancer AND ret	80	0
HAS	20/10/2020	https://www.has-sante.fr/jcms/fc_2875208/en/search-for-a-guideline-an-	NA	12	0

Source	Date	Search details	Search terms	No. hits	Downloaded
		assesment All publications by topic, filtered for respiratory tract diseases -> Respiratory tract cancers			
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0
IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on "Guidance" and published "Technology Appraisal Guidance"	Non small cell lung cancer	41	0
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pralsetinib	0	0
			Selpercatinib	0	0
			Pembrolizumab	28	0
			Pemetrexed	9	0
			Atezolizumab	8	0
			Bevacizumab	12	0
			Carboplatin	0	0
			Cisplatin	0	0
			Paclitaxel	7	0
			Docetaxel	9	0
			Gemcitabine	0	0
			Vinorelbine	3	0
			Nintedanib	5	0
			Nivolumab	28	0
SMC	20/10/2020	https://www.scottishmedicines.org.uk/. Searched terms in search bar	Non small cell lung cancer	62	0

Table 9: Costs and resource use SLR: hand searching methodology and findings for HTA organisations

Source	Date	Search details	Search terms	No. hits	Downloaded
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
G-BA	20/10/2020	https://www.g-ba.de/beschluesse/ Searched terms within decision section, filtered for final reports	Non small cell lung cancer AND ret	80	0
HAS	20/10/2020	https://www.has-sante.fr/jcms/fc_2875208/en/s	NA	12	0

Source	Date	Search details	Search terms	No. hits	Downloaded
		earch-for-a-guideline-an-assesment All publications by topic, filtered for respiratory tract diseases -> Respiratory tract cancers			
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0
IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on "Guidance" and published "Technology Appraisal Guidance"	Non small cell lung cancer	41	0
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pralsetinib	0	0
			Selpercatinib	0	0
			Pembrolizumab	28	0
			Pemetrexed	9	0
			Atezolizumab	8	0
			Bevacizumab	12	0
			Carboplatin	0	0
			Cisplatin	0	0
			Paclitaxel	7	0
			Docetaxel	9	0
			Gemcitabine	0	0
			Vinorelbine	3	0
			Nintedanib	5	0
			Nivolumab	28	0
SMC	20/10/2020	https://www.scottishmedicines.org.uk/. Searched terms in search bar	Non small cell lung cancer	62	0

Table 10: WT NSCLC SLR: hand searching methodology and findings for HTA organisations

Source	Date	Search details	Search terms	No. hits	Downloaded
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0

IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on "Guidance" and published "Technology Appraisal Guidance"	Non small cell lung cancer	41	0
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pembrolizumab	28	0
			Pemetrexed	9	0
			Docetaxel	9	0
			Nivolumab	28	0

A3. Please provide full details of the searches of additional sources referred to in Appendices G.2, H.2, and I.2, including the search strategies or search terms used, date searched, and results.

Table 11: Clinical SLR: hand searching methodology and findings for additional sources

Source	Date	Search details	Search terms	No. hits	Downloaded
Other sources					
University of York CRD website	21/10/2020	https://www.crd.york.ac.uk/CRDWeb/ Searched terms in any field, combined with AND, in DARE, NHS EED, and HTA	"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "NSCLC"	0	0
EuroQoL website	21/10/2020	https://euroqol.org/search-for-eq-5d-publications/ Advanced search in all fields	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
University of Sheffield ScHARRHUD	21/10/2020	https://www.scharrhud.org/index.php?recordsN1&m=search Searched terms in any field	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
INAHTA	21/10/2020	https://database.inahta.org/ Advanced search, terms searched in all field and combined with AND	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0

			"NSCLC" AND "ret"	0	0
National Institute for Health Research (NIHR)	21/10/2020	https://www.nihr.ac.uk/	Non small cell lung cancer	4	0
			Non-small cell lung cancer	4	0
			NSCLC	2	0
			RET	2	0
Reference checking	31/10/2020	Reference checking reviews/included studies	NA	NA	5
Ad hoc	31/10/2020	Google Scholar	NA	NA	0

Table 12: Cost-effectiveness SLR: hand searching methodology and findings for additional sources

Source	Date	Search details	Search terms	No. hits	Downloaded
Other sources					
CEA Registry	21/10/2020	http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx Basic search in "Methods", "Ratios" and "Utility weights"	Methods: non small cell lung cancer	2	0
			Methods: non-small cell lung cancer	76	0
			Methods: NSCLC	107	0
			Ratios: non small cell lung cancer	9	0
			Ratios: non-small cell lung cancer	215	0
			Ratios: NSCLC	275	0
			Utility: non small cell lung cancer	23	0
			Utility: non-small cell lung cancer	415	0
			Utility: NSCLC	512	0
University of York CRD website	21/10/2020	https://www.crd.york.ac.uk/CRDWeb/ Searched terms in any field, combined with AND, in DARE, NHS EED, and HTA	"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "NSCLC"	0	0
INAHTA	21/10/2020	https://database.inahta.org/ Advanced search, terms searched in all field and combined with AND	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
National Institute for Health Research (NIHR)	21/10/2020	https://www.nihr.ac.uk/	Non small cell lung cancer	4	0
			Non-small cell lung cancer	4	0
			NSCLC	2	0

Source	Date	Search details	Search terms	No. hits	Downloaded
			RET	2	0
EconPapers within RePEc	21/10/2020	https://econpapers.repec.org/scripts/search.pf Advanced search, "ret" free text and disease terms in titles and keywords	"Non small cell lung cancer" AND "ret"	15	0
			"Non-small cell lung cancer" AND "ret"	15	0
			"NSCLC" AND "ret"	0	0
Reference checking	31/10/2020	Reference checking reviews/included studies	NA	NA	0
Ad hoc	31/10/2020	Google Scholar	NA	NA	0

Table 13: HSUV SLR: hand searching methodology and findings for additional sources

Source	Date	Search details	Search terms	No. hits	Downloaded
Other sources					
University of York CRD website	21/10/2020	https://www.crd.york.ac.uk/CRDWeb/ Searched terms in any field, combined with AND, in DARE, NHS EED, and HTA	"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "NSCLC"	0	0
EuroQoL website	21/10/2020	https://euroqol.org/search-for-eq-5d-publications/ Advanced search in all fields	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
University of Sheffield ScHARRHUD	21/10/2020	https://www.scharrhud.org/index.php?recordsN1&m=search Searched terms in any field	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
INAHTA	21/10/2020	https://database.inahta.org/ Advanced search, terms searched in all field and combined with AND	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
National Institute for Health Research (NIHR)	21/10/2020	https://www.nihr.ac.uk/	Non small cell lung cancer	4	0
			Non-small cell lung cancer	4	0
			NSCLC	2	0
			RET	2	0
Reference checking	31/10/2020	Reference checking reviews/included studies	NA	NA	0

Source	Date	Search details	Search terms	No. hits	Downloaded
Ad hoc	31/10/2020	Google Scholar	NA	NA	0

Table 14: Costs and resource use SLR: hand searching methodology and findings for additional sources

Source	Date	Search details	Search terms	No. hits	Downloaded
Other sources					
University of York CRD website	21/10/2020	https://www.crd.york.ac.uk/CRDWeb/ Searched terms in any field, combined with AND, in DARE, NHS EED, and HTA	"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "NSCLC"	0	0
INAHTA	21/10/2020	https://database.inahta.org/ Advanced search, terms searched in all field and combined with AND	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
National Institute for Health Research (NIHR)	21/10/2020	https://www.nihr.ac.uk/	Non small cell lung cancer	4	0
			Non-small cell lung cancer	4	0
			NSCLC	2	0
			RET	2	0
EconPapers within RePEc	21/10/2020	https://econpapers.repec.org/scripts/search.pf Advanced search, "ret" free text and disease terms in titles and keywords	"Non small cell lung cancer" AND "ret"	15	0
			"Non-small cell lung cancer" AND "ret"	15	0
			"NSCLC" AND "ret"	0	0
Reference checking	31/10/2020	Reference checking reviews/included studies	NA	NA	0
Ad hoc	31/10/2020	Google Scholar	NA	NA	0

Section B: Clarification on effectiveness data

NICE Final Scope versus Decision Problem

B1. Priority question. The NICE Final Scope defines the population of interest as *"People with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy"*. The same definition is provided in Table 3 (the decision problem) of Document B in the company submission (CS). However, information elsewhere in the CS suggests that the appraisal population is restricted to those with

non-squamous cell NSCLC (Section B.1.1.1 Rationale for selected comparators; Figure 1; and Table 1 of Document B).

(a) Please amend Table 3 of Document B to reflect the narrower population.

The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced NSCLC. The non-squamous histology patients represent 95.8% of patients in the ARROW study and is the population of most interest in this appraisal; however, Roche believes the appraisal population should be all encompassing including squanous patients (in line with the expected licence) rather than restricted to non-squamous, as per the selpercatinib appraisal (1).

In addition, very small numbers of patients with squamous NSCLC were enrolled in the LIBRETTO-001 (selpercatinib) trial and Roche did not present any evidence on using selpercatinib in this tumour histology.

[redacted]; therefore, Table 3 has not been updated to reflect a narrower population.

(b) Please explain to what extent the reported proportion of those with squamous cell NSCLC relates to the United Kingdom (UK) population (p12 of Document B reports 1.4% of patients with squamous cell NSCLC in the ARROW study).

Histologically, NSCLC is divided into three main types: adenocarcinoma, squamous cell carcinoma and large cell carcinoma, with squamous cell carcinomas representing 25-30% of all lung cancers (2). Given that *RET* fusions are seen in 1–2% of patients with NSCLC (3-5) most often in those with adenocarcinoma histology (6), the small proportion (1.4%) of squamous *RET* fusion-positive NSCLC patients enrolled in ARROW is to be expected and reflective of what would be observed in UK clinical practice.

B2. Priority question. The NICE Final Scope describes a series of comparators, stratified according to untreated disease/previously treated disease, tumour histology and biomarker status. The same comparators are shown in Table 3 (the decision problem) of Document B. However, other information indicates that a smaller set of comparators has been used for the appraisal (Tables 1 & 2 and p15-6 of Document B).

Please amend Table 3 of Document B to reflect the narrower set of comparators, including explicit comment on each of the comparators mentioned in the NICE scope, together with rationale for inclusion or exclusion.

Following discussion with NICE and the ERG at the Clarification Call (7th September 2021), it was agreed that Roche would not amend Table 3 (Document B, Section B.1.1.1, page 17) as the rationale for inclusion or exclusion has been provided in Tables 1-2 (Document B, Section B.1.1.1, page 13-5).

However, the ERG requested Roche ensure that for each potential comparator outlined in the Final Scope/Table 3, a rationale for inclusion or exclusion was provided in Tables 1-2 (Document B, Section B.1.1.1, page 13-5). Therefore, these tables have been updated below to reflect the rationale for exclusion for the squamous comparators (Table 15 and Table 16).

Table 15 Untreated comparators suggested in the final scope and justification for inclusion and exclusion in this appraisal – Updated from Document B, Section B.1.1.1, Table 1, page 13-4

Treatment regimen	Population	Inclusion as comparator	Justification
Pembrolizumab monotherapy	Squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score	No	A high proportion of *RET* fusion-positive patients are non-squamous (1.4% of patients enrolled in ARROW were squamous NSCLC). Due to the low incidence of *RET* fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore this appraisal is concentrated solely on non-squamous NSCLC patients. [redacted]
Pembrolizumab with carboplatin and paclitaxel		No	
Atezolizumab monotherapy		No	
Nivolumab plus ipilimumab		No	
Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)	Squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%	No	
Pembrolizumab with carboplatin and paclitaxel		No	
Nivolumab plus ipilimumab		No	

			[redacted].

NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; RET, rearranged during transfection

Table 16 Pre-treated comparators suggested in the final scope and justification for inclusion and exclusion in this appraisal – Updated from Document B, Section B.1.1.1, Table 2, page 14-5

Treatment regimen	Population	Inclusion as comparator	Justification
Atezolizumab monotherapy	Squamous NSCLC PD-L1 <50%	No	A high proportion of *RET* fusion-positive patients are non-squamous (1.4% of patients enrolled in ARROW were squamous NSCLC). Due to the low incidence of *RET* fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore this appraisal is concentrated solely on non-squamous NSCLC patients. [redacted]
Nivolumab monotherapy		No	
Pembrolizumab monotherapy		No	
Docetaxel		No	
Best supportive care		No	
Gemcitabine with carboplatin or cisplatin	Squamous NSCLC PD-L1 >50%	No	
Vinorelbine with carboplatin or cisplatin		No	
Docetaxel		No	
Best supportive care		No	

			[redacted].

NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; RET, rearranged during transfection

B3. Priority question. According to information in the CS (pages 12-3 and Tables 1 & 2 of Document B), the company enlisted the help of an advisory board to support the decisions of which comparators to include and exclude.

(a) Please provide full details of the advisory board's decision-making process in a way the ERG can follow and understand, including: number of participants, declarations of interest of participants, meeting minutes, all other details about the interactions between the company and the advisory board, and the relevant reference (reference 3 listed in Document B appears to be missing).

The advisory board was held on 29th June 2021 and had a panel of six UK consultant oncologists. Obtaining declaration of interests during an advisory board is not standard practice as the meeting is for insight gathering and not promotional in nature.

The aim of the advisory board was to seek advice and gain insights from the panel on the ARROW data presented at ASCO 2021 and how this may impact the current *RET* treatment pathway for patients in the UK. Advice was also sought on competitor data and how it may impact the current treatment/testing landscape in *RET*+ NSCLC. Finally, the advisory board was used to gain feedback on the economic model for the submission. The minutes from the advisory board have been provided in the updated reference pack (7).

(b) Please also provide empirical evidence (independent of the company's advisory board views) of the proportions of patients receiving each of the comparator treatments listed in the final NICE scope in the UK National Health Service (NHS).

The company submission did not provide empirical evidence of the proportions of patients receiving each of the comparator treatments listed in the final scope. The population of interest in the appraisal is *RET* fusion-positive NSCLC. Empirical data, such as market share data, for *RET* fusion-positive patients is not available as in the market share data, *RET* fusion-positive patients are indistinguishable from WT NSCLC patients. *RET* fusion-positive

patients typically present with different characteristics to WT NSCLC patients which therefore may impact treatment decisions. The best way to accurately reflect the proportion of patients receiving each of the comparator treatments listed in the final scope was to gather expert opinion. Roche conducted an advisory board with six leading UK NSCLC clinical experts in order to determine standard of care for *RET* fusion-positive patients and inform the comparator choice for this appraisal (7). Clinicians were asked to discuss and outline the proportion of patients receiving each treatment. Proportions of patients assumed to receive each treatment (which informed the inclusion of comparators in this appraisal and subsequent market shares in the budget impact analysis) were based on clinical expert opinion in these advisory board discussions.

[redacted]

17 [redacted]

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

(c) Please explain the rationale (distinct from any information provided in B3(a) and B3(b) above) for the exclusion of all immunotherapy options in the pre-treated population.

Immunotherapies are typically given as first-line treatment for patients in this indication. As per advice received in the advisory board and NICE guidelines, patients who have received immunotherapies as a first-line treatment are not then offered further immunotherapies in the subsequent lines of therapy (8). Therefore, this class of therapy can be considered inappropriate for patients in the pre-treated setting.

[redacted]

B4. Priority question. In Table 3 of Document B, comparators were separated into untreated and pre-treated patients and according to programmed death-ligand 1 (PD-L1) status.

Please provide subgroup analyses by specific lines of previous therapy and PD-L1 status as specified in the NICE Final Scope for the studies/analyses listed below.

- **the ARROW study**

PD-1/PDL-1 status is only available for total of [redacted] of patients in the safety/unrestricted efficacy population ([redacted]). Therefore, given the large amount of missing data, efficacy outcomes by PD-L1 status are not available. Moreover, stratifying the data by PD-L1 status has little relevance since the efficacy of pralsetinib is not dependent on the presence of the PD-L1 biomarker. This was validated in an advisory board where the clinical experts agreed that PD-L1 status is not relevant for RET-fusion positive patients and therefore would not have any impact on outcomes of these patients.

Efficacy outcomes stratified by different prior regimens is provided below.

Table 18: Efficacy outcomes by prior systemic treatment (Efficacy Population)

	Prior platinum or PD-L1 [redacted]	Prior platinum [redacted]	Prior PD-L1 [redacted]	Prior both platinum and PD-L1 [redacted]	Prior others [redacted]
Best overall response, n (%) Complete response Partial response Stable disease Progressive disease Not evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR, n (%) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CBR, n (%) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCR, n (%) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DOR Median, months 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Median, months 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS Median, months 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CBR, clinical benefit rate; DCR, disease control rate; NR, not reported; ORR, overall response rate; OS, overall survival

- **the indirect treatment comparison (ITC) or make it clear which of the comparators is pertinent to each subgroup, for example by adding an additional column in Table 24**

Table 19 outlines the PD-L1 status and line of therapy of each treatment arm in each comparison presented in the submission.

Table 19: PD-L1 status and line of therapy of each treatment arm in each submission comparison

Setting	Comparison. Pralsetinib vs.	Source for comparator data	Pralsetinib line of therapy	Comparator line of therapy	PD-L1 status used from ARROW	PD-L1 status used to inform comparator arm
Untreated	Pembrolizumab + pemetrexed + chemotherapy	Flatiron	First-line	First-line	ITT	ITT
		WT SLR (9)	First-line	First-line	ITT	ITT
	Pembrolizumab monotherapy	Flatiron	First-line	First-line	ITT	ITT[1]
		WT SLR (10)	First-line	First-line	ITT	PD-L1 ≥50%
Pre-treated	Docetaxel monotherapy	WT SLR (11)	All subsequent lines	Second- and third-line	ITT	ITT
	Docetaxel + nintedanib	WT SLR (12)	All subsequent lines	Second-line	ITT	ITT
	Platinum-based chemotherapy +/- pemetrexed	WT SLR (13)	All subsequent lines	Second-line	ITT	ITT

PD-L1, programmed death-ligand 1; ITT, intention to treat; SLR, systematic literature review; WT, Wild type
[1]The Flatiron dataset was not restricted on PD-L1 status due to a lack of available data. However, it should be noted it is a US database where the licence is restricted to PD-L1≥1%. Therefore, it is likely that the majority of the patients in this dataset would consist of PD-L1≥1% patients

The issue of providing further ITC was discussed with NICE and the ERG at the Clarification Call (7th September 2021). Given the non-availability of robust PD-L1 subgroup data, it was agreed that providing an ITC by line of therapy for the pre-treated population was not required.

- **cost effectiveness analyses or add PD-L1 status to the bulleted list in Section B.3.2.3**

The issue of providing further cost-effectiveness analysis was discussed with NICE and the ERG at the Clarification Call (7th September 2021). Given the non-availability of robust PD-L1 subgroup data, it was agreed that providing a cost-effectiveness analysis by line of therapy for the pre-treated population was not required.

B5. Priority question. In Table 3 of Document B, time-to-treatment discontinuation is specified in the final scope issued by NICE. However, in section B.2.3.2 time-to-off treatment is listed as an exploratory outcome in the ARROW (NCT03037385) study.

Please clarify the difference between the two outcomes and any impact on the analyses this might have had.

The terms 'time-to-off treatment' and 'time-to-treatment-discontinuation' have been used interchangeably and do not represent any additional outcomes or analyses.

Clinical effectiveness section

B6. Priority question: Information in Section/Table B.2.3.2 and Figure 3 indicates that Phase 1 has been completed whereas Phase 2 is ongoing, but details elsewhere suggest that Phase 2 is completed (e.g., B.2.4.3 Efficacy analysis).

(a) Please clarify to what extent Phase 2 has been completed and what the latest data cut-off point is and whether and when further data and analyses will be available.

Recruitment for Phase 2 of ARROW is expected to close in December 2021, with Group 5 (patients with other *RET* fusion-positive solid tumours who have been previously treated with standard of care appropriate for the tumour type) still actively recruiting patients.

The most recent available data from the ARROW study is from the 06 November 2020 data cut; publications of these data are expected in [redacted]. Further data cuts are under discussion but no timelines have been confirmed. Roche Products Ltd will inform NICE and the ERG as soon as any additional data come available during the appraisal. As per below, the data provided within the company submission and additional analyses as part of these clarification questions are the most recently available.

(b) Please provide all relevant results for the latest data cut-off point.

The company submission provides data for the most recent data cut (06 November 2020), with the exception of patient-reported outcomes where data were only available for the previous data cut-off of 18 November 2019. At present, no further data cuts are available, Roche can confirm that all results for the most recent data cut-off point have been provided.

B7. Priority question: Section/Table B.2.3.2 explains that Phase 1 relates to dose escalation whilst Phase 2 involves all patients receiving pralsetinib at a dose of 400 mg four times per day. Please clarify the implications for generalisability to UK clinical practice if Phase 1 data have been used as the basis for analysis.

Only those patients in the Phase 1 cohort who received a starting dose of 400 mg QD, mirroring the Phase 2 dose, were pooled together with the patients in Phase 2 for the efficacy analysis. Therefore, as all patients received the indicated dose, there are no implications on the generalisability to UK clinical practice in including these Phase 1 data in the analysis.

B8. Priority question: Efficacy analyses for the objective response rate (ORR), duration of response (DOR) or disease control rate (DCR) were stated to have been performed on the Measurable disease population, and Efficacy population. However, those for the Efficacy population only seem to have been reported in Section B.2.7 Subgroup analysis.

Please perform and report these analyses on the unrestricted efficacy population and the Efficacy population.

Efficacy analyses for the objective response rate (ORR), duration of response (DOR) and disease control rate (DCR) in the Efficacy Population are provided below. The unrestricted efficacy population is a broader population of patients with *RET* fusion–positive NSCLC and is not defined in the ARROW clinical study protocol. This includes all patients in the safety population with RET fusion–positive NSCLC who were initiated with 400 mg pralsetinib regardless of date of initial dosing. As such, this population is broader than the efficacy population and is considered adequate to assess time-to-event for PFS and OS. No further analyses for this population has been conducted.

Overall response rate

In the overall efficacy population, ORR was [redacted] (n=233). [redacted].

- *Treatment-naïve subgroup (n=75):* [redacted]

Prior systemic treatment subgroup (n=158): ORR was [redacted]

Duration of response

Among all 150 patients in the RET fusion–positive NSCLC efficacy population with a confirmed response, median DOR was [redacted]) with [redacted] of the responding patients censored. KM estimates for ongoing response were [redacted]) at 6 months, [redacted]) at 9 months[redacted] at 12 months, and [redacted]) at 18 months.

- Treatment-naïve subgroup: among the 54 patients with a confirmed response, [redacted]) with [redacted] of the responding patients censored. KM estimates for ongoing response were [redacted]

  Prior systemic treatment subgroup: among the 96 patients with a confirmed response, median DOR was [redacted] with [redacted] of the responding patients censored. KM estimates for ongoing response were [redacted]

Disease control rate

DCR in patients with RET fusion–positive NSCLC in the overall efficacy population was [redacted] In addition, there were no clinically relevant differences in DCR between the overall population and the prior systemic treatment subgroup of patients.

- Treatment-naïve subgroup (n=75): DCR was [redacted]
- Prior systemic treatment subgroup (n=158): DCR was [redacted]

B9. Priority question: Subgroup analyses by PD-L1 status were presented only for ORR.

Please provide these for all outcomes i.e., DOR, DCR, progression-free survival (PFS) and overall survival (OS).

This question was discussed with NICE and the ERG at the Clarification Call (7th September 2021). The data provided in Document B (Section B.2.7, page 64) is not subgroup analysis by PD-L1 status, instead the data provided is by prior PD-L1 therapy. As highlighted in the response to question B4, efficacy outcomes by PD-L1 status are not available; however, data by prior PD-L1 therapy are provided in Table 18 as part of the response to B4.

B10. Priority question. As per section B.2.3.2, only central nervous system (CNS) activity was assessed by blinded independent central review (BICR).

Please provide data using BCIR for the remaining outcomes.

While the company submission only highlights that CNS activity was assessed by BICR, Roche can confirm that all endpoints involving response assessment in the ARROW study were based on BICR data, with investigator assessments also analysed using the same analysis method for supportive analyses. Furthermore, data in the ITCs used BICR assessments by default. As such, BICR data for the remaining outcomes have already been provided in the company submission.

B11. Priority question. In section B.3.4.2 of Document B, health-related quality-of-life (HRQoL) data "were not viewed as robust enough to inform decision making". The Evidence Review Group (ERG) also notes that HRQoL data were not reported in the clinical effectiveness section.

Please justify the selection of the health state utility values from the literature, and implications for patients and clinicians.

[redacted]

A common approach in NICE appraisals in the absence of HRQoL data elicited from the trial population is to use publically available utilities from previous NICE submissions. Health state utility values selected for use for the untreated and pre-treated economic models were previously approved by NICE committees and represented the closest available evidence to represent *RET* fusion-positive advanced NSCLC (14-16). Further details on health state utilities selected are provided in the response to clarification question C8.

A range of health state utility values were assessed for inclusion in the base case analysis. Utilities were selected based on comparability with the current appraisal population. Utilities selected generally represented the middle of the range of available utilities. A variety of utilities were explored in the scenario analysis and results were shown to not be sensitive to the choice of health state utility values.

The impact of age and sex-related disutility have been considered in the economic model with disutilities decreasing as patients in the model age (Document B, Section B.3.4.5, pages 155-6).

B12. Priority question. As per section B.2.4.3.3, patient reported outcomes (PROs) are only available for the 18th of November 2019 cut-off point.

Please provide the relevant PRO for the most recent cut-off point.

As discussed in B.6 (b), patient-reported outcomes data is only available for the primary analysis (18th November 2019 data cut-off) as patients completed the EORTC QLQ-C30 questionnaire on day 1 of Cycles 1 through 12, therefore no further data was collected beyond this. As such, the PRO data previously provided within the company submission is the most recent and only dataset available.

B13. Priority question. As per section B.2.3.1, Group 8 (NSCLC patients from China only) contribute data in the safety analysis but not in the efficacy analysis.

Please include all the relevant data in the efficacy analysis.

Efficacy and safety of pralsetinib in Chinese patients with advanced *RET* fusion-positive NSCLC after platinum based chemotherapy (Zhou et al. 2021) was presented at IASLC 2020 and is provided in the reference pack (17). However, data from Group 8, i.e. Chinese patients was selectively excluded from the efficacy analysis to ensure that the patient characteristics better reflected that of the UK population.

B14. Please specify whether patients with Eastern Cooperative Oncology Group (ECOG) status above 1 would have been offered pralsetinib.

The key inclusion criteria of the ARROW trial stated an ECOG of PS 0–1; however, patients with a baseline ECOG PS score of 2 were allowed up until protocol amendment 4.1. Therefore, 6 patients (2.8%) with an ECOG PS score of 2 were enrolled and received pralsetinib.

B15. In Table 8 of Document B, 49.8% of the patients had prior cancer related surgeries/ procedures.

Please specify which therapies were administered and when.

Full details of the surgeries/procedures administered and timelines of these are provided in the reference pack of the submission as a confidential data on file.

External validity

B16. Priority question. Table B.2.3.2 in Document B explains that the ARROW study is international with some patients being recruited from UK settings. Furthermore, Table 8 of Document B indicates that 39.5% of the ARROW efficacy population is Asian.

(a) Please confirm the proportion of patients recruited within UK-based study sites.

Thirteen patients were recruited into the ARROW trial from UK-based study sites.

(b) Please discuss the implications for generalisability to UK clinical practice of including non-UK patients.

ARROW is a Phase 1/2, multicentre, non-randomised, open-label, multi-cohort study, with the Phase 2 dose expansion phase conducted in 13 countries. Given the international nature of the study it is not unexpected that the enrolled population includes patients of different ethnicities. While including patients from countries with different treatment practices is a limitation of the study from the perspective of the current appraisal, it is common practice to use evidence from Global registrational clinical trials in reimbursement submissions. Furthermore, UK clinical experts confirmed to Roche that the enrolled population is similar to other oncogenic driver clinical trials (7) which have been used as evidence sources for UK HTA (18). Therefore, the study population can be considered generalisable to UK clinical practice and applicable for decision making.

(c) Please clarify to what extent the distribution of different ethnic groups within the ARROW study is generalisable to the UK population.

Although the proportion of Asian patients enrolled in ARROW is high (38%), clinical experts raised no concerns about the distribution of ethnicities in the enrolled population and overall they agreed that the study population reflected patients seen in UK clinical practice (7). Moreover, the distribution of ethnic groups within the ARROW study is consistent with other studies in *RET* fusion-positive NSCLC; for instance, in the LIBRETTO-001 study, the proportion of Asian patients enrolled in the previous platinum chemotherapy and previously untreated groups was 38% and 18% respectively (19).

(d) Please provide results for patients similar to the population relevant for this appraisal (i.e., NHS patients in England).

As the population is already the most similar population available for *RET* fusion-positive patients in the UK, no further population from ARROW can be provided.

SLR of pralsetinib studies (Document B)

B17. Priority question. As per Table 7 of Appendix D, some relevant studies were excluded.

Please justify the exclusion of Hegde 2019, O'Leary 2019, Ribeiro 2019, Takeda 2019, and Yang 2019.

Table 20: **Further rationale for exclusion of studies**

Study	Citation	Rationale
Hegde 2019	Responsiveness to immune checkpoint inhibitors in *RET* dependent cancers. Cancer Research. 2019. 79 (13 suppl). Abstract 4997	Data are reported for patients receiving immune checkpoint inhibitor therapy versus non-immune checkpoint inhibitor therapy, but were not reported for the subgroup of patients with NSCLC
O'Leary 2019	Rearranged During Transfection Fusions in Non-Small Cell Lung Cancer. Cancers (Basel). 2019;11(5):620. Published 2019 May 3. doi:10.3390/cancers11050620	This is a narrative review, not a primary publication. The reference list was checked to ensure that any relevant primary publications had been considered for inclusion
Ribeiro 2019	P2.14-67 Metastatic *RET*-Rearranged Lung Adenocarcinomas Treated with Alectinib: Retrospective Analysis of a Single Institution. Journal of thoracic oncology. 2019. 14 (10 Supplement):S857-S858.	This was an abstract which was superseded by a full publication: Ribeiro 2020 (and did not report any unique data) (20). The full publication was included in the SLR.
Takeda 2019	Successful long-term treatment of non-small cell lung cancer positive for *RET* rearrangement with pemetrexed. Onco Targets Ther. 2019;12:5355-5358. Published 2019 Jul 8. doi:10.2147/OTT.S211582	This is a single patient case report and case reports were excluded from the SLR.
Yang 2019	P2.14-01 Real World Treatment Outcomes in Chinese Patients with *RET*-Rearranged Lung Cancer Journal of thoracic oncology. 2019. 14 (10 Supplement):S829.	This abstract publication reports a retrospective real-world analysis of a web-based patient registry and hospital chart review in China. Whilst there are limited details of interventions, no outcome data are reported in patients treated with a specific intervention.

NSCLC, non-small cell lung cancer; RET, rearranged during transfection; SLR, systematic literature review

B18. Section B.2.5 of Document B indicates that there was no quality assessment of the ARROW study, and it is not clear why this was not done.

Please include a quality assessment of the ARROW study using a suitable critical appraisal tool e.g., Downs & Black (as used in Table 10 of Appendix D, Downs and Black checklist for non-randomised studies).

A quality assessment of the ARROW study was not conducted as this study was included on the basis of the clinical study report. A quality assessment of the study (based on the Lancet

Oncology manuscript by Gainor et al pblished in July 2021 (21)) using the Downs & Black tool is provided below.

Table 21: Quality assessment of ARROW (Downs & Black)

Question No.	Question	ARROW
1	Is the hypothesis/aim/objective of the study clearly described?	Yes
2	Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes
3	Are the characteristics of the patients included in the study clearly described?	Yes
4	Are the interventions of interest clearly described?	Yes
5	Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes
6	Are the main findings of the study clearly described?	Yes
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes
9	Have the characteristics of patients lost to follow-up been described?	No
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear
13	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Unclear
14	Was an attempt made to blind study subjects to the intervention they have received?	No
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes
16	If any of the results of the study were based on 'data dredging', was this made clear?	NA
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes
19	Was compliance with the intervention(s) reliable?	Yes
20	Were the main outcome measures used accurate (valid and reliable)?	Yes

21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA
23	Were study subjects randomised to intervention groups?	No
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unclear
26	Were losses of patients to follow-up taken into account?	Unclear

B19. As per Table 5 of Appendix D, a set of inclusion criteria is listed.

Please specify which exclusion criteria, if any, were applied.

No explicit exclusion criteria were applied. Citations that fell out of the scope of the inclusion criteria were excluded from the systematic review, i.e. publications not in adult patients with stage III/IV RET+ NSCLC, not including pharmacological interventions for NSCLC or any of the outcomes listed. Publications not related to the included study design types, i.e. review articles were also excluded.

B20. Appendix D of the CS states: "*Where necessary, calculations to obtain values for any subsequent matching adjusted indirect comparison (MAIC) analyses can be conducted by the statistician*".

Please provide full details of all calculations undertaken.

The quoted sentence above is generic for descriptions on MAIC methodology. In this instance no calculations were necessary. Further, in the clinical SLR (Appendix D), no MAICs were used that informed the current economic analysis.

In the WT SLT (Appendix L), again no calculations were necessary. For the naïve treatment comparisons, no baseline characteristic data were used and so there was no need to calculate any percentages for example. Similarly, as individual patient data were used for the propensity scoring analysis, no additional calculations were required.

B21. Appendix D of the CS states: "*data extraction was conducted by an analyst and all data inputs were independently checked against the source document by a second analyst*".

Please discuss potential biases arising from not extracting data independently by two reviewers.

Although the second independent analyst checked the extractions of the first reviewer, the process undertaken by the second reviewer mitigated bias by applying the robust steps below:

- Review the publication(s) associated with the study for extraction, highlighting any relevant data for extraction
- Check that all data from the publication(s) had indeed been extracted into the data extraction table (DET) in the correct cell (in this way, any data 'missed' by the first extractor was included in the Excel sheet – any additional data extracted were highlighted and checked by the first extractor [any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser])
- Check that the correct values had been extracted (any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser)

Therefore, the triangulation process undertaken was comprehensive and robust ensuring that all relevant data had been extracted from the publication(s).

SLR underpinning the matching adjusted indirect comparison (MAIC) (Appendix D)

B22. The ERG noted restriction to English language publications. Table 5 in Appendix D (study eligibility criteria for the main systematic literature review [SLR]) and Table 40 in Appendix L (study eligibility criteria for the SLR of wild type NSCLC) both indicate that study selection was restricted to English language publications and publications in other languages with an abstract in English.

For both instances, please explain this restriction and explain the likely impact of excluding non-English papers.

Across both reviews, the restriction to English language abstracts was applied at the title/abstract screening phase and not within the search strategy itself and therefore any non-English language papers identified in the search would have been reviewed at the title/abstract screening stage and assessed for inclusion.

A total of four citations were excluded using the 'language' exclusion code during title/abstract screening for the clinical SLR presented in Appendix D.

- Iwama E, Takayama K, Baba E, Nakanishi Y. [Personalized medicine in non-small-cell carcinoma]. Fukuoka Igaku Zasshi. 2014 Mar;105(3):57-66. Japanese. PMID: 25000657.

- Matěj R, Rohan Z, Němejcová K, Dundr P. Molekulární patologie plicních karcinomů pro rutinní praxi - update 2017 [Molecular pathology of lung cancer in routine diagnostic practice: 2017 update]. Cesk Patol. 2017 Winter;53(4):159-166. Czech. PMID: 29227119.
- Jin LL et al. The progress of KIF5B-RET fusion gene in non-small cell lung cancer. Chinese Journal of Tuberculosis & Respiratory Diseases. 2013. 36(7):524-6
- Wang J et al. Targeted therapy for advanced non-small cell lung cancer in the elderly. Chinese Journal of Lung Cancer. 2009. 12(7):821-825.

It is clear from the title of these citations that they were not primary clinical studies that would have reported relevant outcome data for inclusion in the meta-analysis feasibility and therefore there was no impact from the exclusion of non-English publications.

For the WT SLR (Appendix L), no citations were excluded at title/abstract screening on the basis of language (22). However, two Chinese language publications were carried forward to full publication review. The first was excluded due to the lack of relevant outcome data (and the line of therapy was unclear), as the primary focus of the study was to report the serum levels of VEGF and endothelin and immunologic function:

- Chu W et al. The Effect of Pemetrexed Combined with Cisplatin for Treatment of Patients with Non-small Cell Lung Canceronimmunologic Function. Anti-Tumor Pharmacy, 2017, 7(5), 581-585

The second was considered for inclusion in the ‘second-line platinum-based chemotherapy in combination with pemetrexed or paclitaxel’ evidence base:

- Wang C et al. Comparison of docetaxel and pemetrexed combined with platinum in treatment of NSCLC after failure of gefitinib therapy. Journal of Practical Oncology. 2017. 32(2):164-167.

However, this trial enrolled a smaller number of patients (n=110) than the two trials included in the pooled analysis which were selected for consideration in the meta-analysis (GOIRC 02-2006 and NVALT7; n=479) and it was assumed that the enrolled patients would have been predominantly, if not exclusively Chinese, limiting the external validity of the results. Therefore it was decided that translation of this paper into English was not required.

B23. Page 12 of Appendix D in the CS provides brief details about the approach used for data extraction.

Please explain how disagreements about data extraction between the two analysts were resolved.

Any disagreements on the extractions between the two analysts which could not be resolved through consensus were taken to a third party (strategic advisor) for resolution.

SLR for wild type (WT) NSCLC (Appendix L)

B24. Table 40 (eligibility criteria for the SLR) of Appendix L explains that studies published in 2017 and later were included and that *"Studies published pre-2017 were of interest"*. It is not clear from this what the distinction is between studies published before 2017 and during/after 2017 in terms of eligibility for the SLR.

Please clarify this and state clearly whether the pre-, during, and post-2017 studies were eligible for inclusion.

To address data gaps identified for comparators of interest, Roche expanded the scope of a previous SLR to identify RCTs conducted in patients with wild-type (WT) NSCLC (i.e., patients with tumours without a gene mutation or rearrangement or unknown mutation status) treated in either the first- or second-line and beyond setting. However, due to the amount of published clinical data available for the WT population, a *de novo* SLR was not conducted; rather a previously commissioned SLR conducted to identify all available second-line and further line pharmacological treatments used for locally advanced/metastatic NSCLC was leveraged (database searches conducted March 2017) . Although this SLR was restricted to studies conducted post second line, the search strategy employed was not restricted by line of therapy. Therefore, this previous search strategy was used to identify potentially relevant RCTs published post 2017.

The following steps were undertaken to identify relevant RCTs published pre-2017 for the updated SLR.

Second-line and beyond RCTs

- Review of the 2017 data extraction file to identify RCTs investigating an intervention of interest

First-line RCTs

- Review of the 'Abstract and full text screening' tab of the 2017 data extraction file to identify those studies excluded as first-line. The title/abstract of these RCTs were then screened to confirm whether they met the inclusion criteria for the current SLR

All relevant studies, pre-, during- and post-2017 were eligible for inclusion

Indirect and mixed treatment comparisons

B25. Priority question: The company have implemented a stepwise approach to selecting comparator studies, as shown in Figure 14 of Document B. It is unclear why pooled analyses or studies with the largest sample size were the only criteria after the step where population characteristics were aligned with the ARROW study.

(a) Please provide a list of studies excluded by lack of pooling or smaller sample size.

The 131 studies identified in the WT SLR reported 137 treatment arms investigating one of the interventions of interest. These are outlined in Table 22 along with their reason for exclusion from consideration at the assessment stage before the stepwise approach.

Table 22: Studies considered for selection in WT SLR for each comparator

Setting	Comparator	Number of potentially relevant studies	Studies excluded	Reason for exclusion
Untreated	Pembrolizumab + pemetrexed + chemotherapy	5	3	Abstract only studies: 2; second-line only studies: 1
Untreated	Pembrolizumab monotherapy	8	5	Second-line only studies: 5
Untreated	Platinum-based chemotherapy + pemetrexed or paclitaxel	68	68	Comparator not applicable for NICE appraisal
Pre-treated	Docetaxel monotherapy	44	0	--
Pre-treated	Docetaxel + nintedanib	1	0	--
Pre-treated	Nivolumab monotherapy	7	7	Comparator not applicable for NICE appraisal
Pre-treated	Platinum-based chemotherapy +/- pemetrexed	4	2	Abstract only studies: 1; non-English language studies: 1

SLR, systematic literature review; WT, Wild type

Table 23 displays the studies that were considered for selection at the stepwise approach stage outlined in Document B, Section B.2.9.4, page 70.

- For pembrolizumab + pemetrexed + chemotherapy, KEYNOTE-189 (n=410) was selected over KEYNOTE-021 (n=60) based on sample size
- For pembrolizumab monotherapy, this is only reimbursed by NICE in this setting in the PD-L1 ≥50% population. Two trials identified reported the relevant PD-L1 ≥50% population. In these two studies, KEYNOTE-042 (n=299) was selected ahead of KEYNOTE-024 (n=154) based on sample size

- For docetaxel monotherapy, two studies had individual patient level data available. The OAK trial (n=612) was selected ahead of POPLAR (n=142) based on sample size. Further, OAK represented a Phase III trial compared to POPLAR which represented a Phase II trial
- For docetaxel + nintedanib, the LUME-Lung 1 was selected for use as this was the only study available
- For platinum-based chemotherapy +/- pemetrexed, one study contained both the two available trials in a pooled analysis therefore this was selected for use in the comparison and no trials were excluded

Table 23: Studies selected using the stepwise approach in WT SLR for each comparator

Setting	Comparator	Trials available for stepwise approach	Trial selected	Rationale for selection
Untreated	Pembrolizumab + pemetrexed + chemotherapy	KEYNOTE-189; KEYNOTE-021	KEYNOTE-189	Sample size
	Pembrolizumab monotherapy	KEYNOTE-598; KEYNOTE-042; KEYNOTE-024	Most similar histology status	PD-L1 status and sample size
Pre-treated	Docetaxel monotherapy	44	OAK	Individual patient data available and sample size
	Docetaxel + nintedanib	LUME-Lung 1	LUME-Lung 1	Only one available
	Platinum-based chemotherapy +/- pemetrexed	GOIRC 02-2006 + NVALT7; NVALT7	GOIRC 02-2006 + NVALT7; NVALT7	Pooled analysis of both studies available

SLR, systematic literature review; WT, Wild type

(b) Please provide a justification as to why no other characteristics might have been suitable to perform the comparison.

For the sample size criterion, this was implemented as studies with a larger sample size lead to narrower confidence intervals, more certainty in results and therefore a more robust comparison. The sample size criterion was applied in three instances. Two of these instances were in the untreated setting where Flatiron individual patient level data was available and the comparison was not used in the base case analysis. In the case of docetaxel monotherapy, OAK represented a Phase III trial compared to POPLAR which represented a Phase II trial. In all cases the study selected represented a substantially larger sample size than the alternative choice leading to reduced uncertainty and more robust results.

The use of a pooled analysis as a selection criterion was only applied for platinum-based chemotherapy +/- pemetrexed. As only two studies were available, it is considered more robust to select a pooled analysis comprising all the available data rather than select a single study.

Because the two criteria explain above allowed for the selection of one trial per study, there was no need to consider further characteristics.

(c) Please provide alternative analyses with all comparators for which no individual patient data were available using the next largest study (or studies) to the ones already used.

A naïve comparison has been performed using data identified for two additional first-line comparator studies; KEYNOTE-021 (pembrolizumab + pemetrexed + chemotherapy) and KEYNOTE-024 (pembrolizumab monotherapy). For the other two comparisons where no individual patient data was available, no next largest study existed (as per response to B25a).

Analyses were conducted for both OS and PFS. No individual patient data were available for either of these two studies, however, published Kaplan-Meier curves were reported for both OS and PFS outcomes.

Consistent with the approach adopted for the existing naïve comparisons presented in the submission (Document B, Section B.2.9.4, pages 67-80), published Kaplan-Meier curves were digitised to recreate virtual individual patient data, which was combined with the untreated patient cohort from the ARROW trial. A Cox regression model was then fitted to the data to estimate a measure of comparative efficacy in the form of a hazard ratio (HR) and corresponding 95% confidence interval (CIs).

Both comparator studies reported PFS using Independent Review Committee (IRC)-assessment and therefore, this definition of PFS from the ARROW trial was selected to match the assessment used in both comparator studies.

A summary of the results from these naïve comparisons is presented in Table 24, which shows that pralsetinib retains statistically significant benefit over pembrolizumab monotherapy for both OS and PFS (95% CI < 1). Pralsetinib also retains numerical superiority over pembrolizumab + pemetrexed + chemotherapy for OS, although the comparison is statistically non-significant. The comparison for PFS is also not statistically significant. However, it should be noted that the sample size for pembrolizumab patients in KEYNOTE-021 in low (n=60).

Table 24: Summary of naïve comparisons with KEYNOTE-021 and KEYNOTE-024 for OS and PFS

Study	Comparison	OS HR [95% CI]	PFS HR [95% CI]
KEYNOTE-021	Pralsetinib vs pembrolizumab + pemetrexed + platinum	[redacted]	[redacted]
KEYNOTE-024	Pralsetinib vs pembrolizumab monotherapy	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Notes: Results are presented for the comparison between pralsetinib versus comparator under investigation; HR<1 favours pralsetinib; HR>1 favours comparator under investigation;

Bold** denotes statistical significance at 5% level.

The Kaplan-Meier curves for OS and PFS for both comparisons are presented in Figure 1 and Figure 2.

Figure 1: Kaplan-Meier curves for OS and PFS for pralsetinib (ARROW trial data) vs pembrolizumab + pemetrexed + chemotherapy (KEYNOTE-021)

[redacted]

OS, overall survival; PFS, progression-free survival

Figure 2: Kaplan-Meier curves for OS and PFS for pralsetinib (ARROW trial data) vs pembrolizumab monotherapy (KEYNOTE-024)

[redacted]

OS, overall survival; PFS, progression-free survival

(d) Table 25 of Document B reports the proportion of participants with adverse events for the overall safety population of the ARROW study (all tumour types) and separately for participants with *RET* fusion-positive NSCLC but no estimates from treatment comparisons are presented. Please provide an indirect treatment comparison for adverse events for the safety population of participants with *RET* fusion-positive NSCLC.

Generally, indirect treatment comparisons of safety outcomes are challenging. This is mainly driven by differences in the follow-up time and duration of treatment across trials and treatment arms (e.g., due to deaths and treatment discontinuations). Additionally, it is not recommended to undertake detailed safety comparisons considering simply reported occurrences of AEs, and the frequency of AEs alone is not likely to reflect their impact on patients' well-being, with considerable variability in the effects of different AEs and their management on patients' clinical status and daily functioning.

Considering the pool of comparators being used for pralsetinib assessment, there are different mechanisms of action, different treatment durations, follow-up times and trial

designs which make a comparison potentially misleading. For example, in LUME-Lung 1 the median duration of treatment was 3.4 months while in ARROW for the safety population that was 9.46 months (12).

Additionally, very limited data is available for the comparators studies with most of the adverse events being grouped (e.g. any adverse event, any treatment related adverse event), which does not allow the differentiation in the safety profiles of the different treatments. This is worsened by the fact that mainly naive comparison would have been possible with very few safety endpoints per comparator, and not allowing for proper adjustments.

In light of the above limitations of comparative safety analyses, Roche feel that this is not an appropriate analysis to conduct in this setting.

Nonetheless, when descriptively assessing toxicity profiles in comparison to standard of care treatment options in advanced NSCLC, pralsetinib demonstrates an acceptable safety and tolerability profile. Pralsetinib is associated with good manageability of adverse reactions that are reversible in their majority and with low discontinuation rates due to related AEs.

B26. Propensity score matching. Please:

(a) **elaborate whether the variables used in the propensity score weighting used to obtain the HRs are sufficient and appropriate;**

Baseline characteristics captured for both the ARROW trial data and the Flatiron database that are explicitly adjusted for in the analyses include age, sex, smoking status, ECOG, time from initial diagnosis to first dose, stage at diagnosis and race. Variables were identified as key prognostic factors in advanced NSCLC. The variables included were shared with clinical experts at an advisory board who confirmed their importance and confirmed that, after matching the untreated ARROW populations and the Flatiron comparator, the data sets were clinically well matched.

(b) **consider adding a variable representing Body Mass Index (BMI) or similar to account for potential underlying general health risks between the populations (or justify the decision not to do so);**

The population available in the unrestricted efficacy population for untreated ([redacted]) and pre-treated ([redacted]) are relatively small. Therefore, the analysis is limited in the number of covariates that can be added and there exists a risk of overfitting the model. In a comparable analysis in the selpercatinib appraisal, identical variables were used with the addition of EGFR+, PD-1/PD-L1+, RET+, other mutations (ALK, ROS1, BRAF, KRAS) variables and the

ERG cautioned a risk of overfitting the model (16). Given constraints on the number of variables that could be included, BMI was excluded from use as a variable in favour of the seven variables included.

(c) **report the "effective sample size" as described in section 2.9.5: “calculated by taking the square of the sum of all weights divided by the summation of each of the weights squared" as these appear to be missing from the results section, in particular Tables 21 and 22;**

For the comparison for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy in the Flatiron cohort, the effective sample size in the comparator cohort is [redacted]. For the comparison for pralsetinib vs. pembrolizumab monotherapy in the Flatiron cohort, the effective sample size in the comparator cohort is [redacted].

(d) **provide the reasoning why a threshold of three was chosen for "trimming" of the propensity scores.**

All propensity score descriptive statistics below are based on weights trimmed at a threshold of three. The threshold was based on visual inspection of the distribution of weights.

(e) **provide descriptive statistics about the logistic propensity score model, at least statistics describing the fit of the model; and**

After examining the role of model fit statistics for the propensity score model, several conclusions were reached that altogether induced the exclusion of such measures in the analyses. First, the primary goal of the propensity score model is to assess the conditional probability of the assigned treatment given a restricted set of covariates with the analytical goal to improve balance of confounders between the treated and untreated cohorts. The crucial step in this approach is the assessment of the role of balance by treatment groups by common baseline covariates with respect to reducing potential confounding bias in the eventual outcome model estimates.

Model fit, however, as pertaining to certain statistics, specifically the c-statistic, has historically been used to assess goodness-of-fit in the propensity score model. The c-statistic assesses the discriminatory power to classify patients in one treatment group versus another. Unfortunately, the propensity score model fit and c-statistic could be intentionally made to have a near perfect discriminatory score by including more variables in a model subset regardless of their relevance to the subject knowledge for the assessed problem. As per Westreich, it could lead to inclusion of covariates strongly related to the treatment but unrelated to the outcome, which increases the c-statistic and subsequent model inclusion (23). The inclusion of such variables could lead to distributions of propensity scores with

relatively little overlap between the treated and the untreated. Since the treatment-outcome effect is estimated in subjects with the same propensity score, data that fall outside a common range of the propensity score distributions in treated and untreated are typically lost for the second stage of a propensity score analysis. Subjects are either excluded from analyses or they cannot be matched between treatment groups.

A separate simulation study by Weitzen et al. mentioned that the c-statistic has no relationship with residual confounding in treatment effect estimates (24). Additionally, Austin et al. mentioned the 'c-statistic provides no information as to whether the propensity score model has been correctly specified' (25).

It is based on these multiple reviews and simulation studies that Roche advise focusing on the metric of balance and prior subject knowledge for the ultimate reduction of confounding bias in the estimation of treatment effects.

(f) **provide descriptive statistics about the predicted propensity scores (e.g., mean/median/min/q1/q3/max predicted score) and further elaborate how well the populations matched.**

Table 25 displays the descripted statistics about the predicted propensity scores for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy in the Flatiron cohort. Table 26 displays the descriptive statistics about the predicted propensity scores for pralsetinib vs. pembrolizumab monotherapy in the Flatiron cohort. For both comparisons, the poor overlap is not very surprising given the very notable differences in variables such as smoking history and age, and is consistent with the discussion based on the discussion in the main analysis. However, the healthy sample size of the Flatiron cohort still allowed for a decent number of good matches.

Table 25: Descriptive statistics about the predicted propensity scores for the Flatiron comparison between pralsetinib and pembrolizumab + pemetrexed + chemotherapy in untreated population

	Pralsetinib	Pembrolizumab + pemetrexed + chemotherapy
Mean (std)	[redacted]	[redacted]
Median (25th, 75th)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Table 26: Descriptive statistics about the predicted propensity scores for the Flatiron comparison between pralsetinib and pembrolizumab monotherapy in untreated population

	Pralsetinib	Pembrolizumab monotherapy
Mean (std)	[redacted]	[redacted]
Median (25th, 75th)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Section C: Clarification on cost-effectiveness data

Model structure

C1. The model was implemented using the Partitioned Survival Model (PSM) approach, with a cycle time of one month. Please clarify:

(a) why this model type was chosen over a State Transition Model (STM), and how this model type "is expected to accurately reflect disease progression" (Section B.3.2.2).

A PSM was selected as this approach has been used and deemed appropriate in previous advanced NSCLC NICE appraisals (15, 26-29). A PSM is technically straightforward to implement, intuative to understand, directly uses the available trial data and means results are consistent with previous NICE appraisals. A key driver of results in this economic model is survival in the PD health state and the PSM is superior to state transition models at modelling survival in the PD health state. PSMs are the most commonly used model structure in oncology appraisals.

PFS and OS were secondary endpoints in the ARROW clinical trial and inform the health states in the PSM (PF, PD and death). Further, these endpoints align with the key aims of treatment (from patient, clinician and NHS perspective) of *RET* fusion-positive NSCLC patients in clinical practice – to delay disease progression and to extend survival.

(b) why a model resolution of 1-month was chosen instead of a 1-week resolution which was the choice in previous appraisals (as stated in Table 36: Features of the economic analysis).

A 1-month cycle was deemed a sufficient length of time to account for changes in PFS and OS. The monthly cycle length allows for ease of interpretation of model engine outputs and allows for accurate modelling of outcomes without impairing computational efficiency by having many cycles in the model engines. Half cycle corrections have been used to mitigate any impact of usage of a longer cycle length.

The 1-month cycle length was also validated against previous NICE appraisals in advanced NSCLC where the cycle length was deemed appropriate (27).

C2. Please elaborate why the distribution choice for uncertainty around the parameters of the survival extrapolations was Multivariate Normal, and whether this is a realistic assumption.

The current appraisal uses Cholesky decomposition matrices to calculate probabilistic estimates of the survival parameters used to inform the survival curves which model clinical efficacy in the PSA. Cholesky decomposition matrices are used to interdependently sample parameters in a distribution. This method of sampling survival parameters is commonly used in oncology appraisals (1, 27).

Efficacy

C3. Priority question. Related to question B3 above, the selection of parametric survival curves relied heavily on clinical expert opinion. Please provide:

(a) Full details of the reasoning of the advisory board members in preferring one parametric distribution over another (OS, PFS, and time to discontinuation (TTD) for both populations).

Full details for the reasoning of the clinical experts in the advisory board are provided in the advisory board minutes which have been provided in the reference pack (7).

(b) Justification on why only the Exponential and Weibull distributions were included in the base case and scenario analyses. Especially because the chosen distributions are not always the most conservative choice facing the extensive uncertainty, nor do they always align best with the experts' advice. In particular, following the results from for instance Tables 42, 45, 51 and 54 in Document B, other distributions (such as the log-logistic and/or log-normal distributions) appear to align more with the experts' opinion.

For each of the six curve selections, a base case curve selection was made and one alternative curve selection was used for scenario analysis. There was no specific preference for the selection of the exponential and Weibull curves, curve choice was made in line with NICE guidance (30).

An advisory board was held with clinical experts to assist with curve selection. Clinical experts were asked to predict clinically plausible ranges of survival before seeing extrapolated curves. Clinical experts repeatedly stated difficulty predicting a numerical range of plausible survival at landmark points in a population characterised by RET fusion positive NSCLC. In some instances these did not realistically align with ARROW data (e.g. ARROW trial TTD 28.5% at 2-years vs. clinical experts' predicted plausible range of 30-35% at 3-years). Clinical experts were more comfortable making recommendations for curve selection when shown visual extrapolations similar to those presented in the response to C5. Therefore, more weight in curve selection recommendation was given to clinical experts'

recommendations made picking visual fit from extrapolations rather than aligning curve extrapolations with the range numerical deemed clinically plausible ex-ante.

Clinical experts stated that they expected PFS and TTD to align closely. Further, clinical experts stated they expected similar PFS and TTD between the untreated and pre-treated settings.

Advice of the clinical experts was that the exponential curve, as one curve in the middle of the presented extrapolations represented a suitable fit for both PFS. In the absence of available long-term *RET* fusion-positive follow up data/NICE appraisals, it is possible to use what the committee have deemed an acceptable level of PFS/TTD in previous NICE appraisals in comparable populations. The 5-year TTD of 4% predicted by the exponential model is comparable to what the NICE committee has deemed acceptable in recent appraisals in comparable populations including 5.8% (for 5-year TTD for entrectinib in line-agnostic ROS1-positive advanced NSCLC as modelled by the exponential curve) and 3.2% (for 5-year PFS for osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer as modelled by the generalised gamma curve) (27, 31).

(c) A reference or further explanation/substantiation for the statement on page 117 of Document B that for Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) 'a difference of five or more …. is generally considered meaningful'

This is a general rule of thumb within the field and therefore no references can be provided for this. Small differences between in distributions' AIC or BIC values can be considered negligible and therefore not suitable criterion to determine curve selection as the difference in fit is marginal.

C4. Priority question. Regarding hazard ratio estimates:

(a) Please provide, and implement in the economic model, HR estimates for the chart review in RET fusion-positive population which was estimated to be completed in August.

[redacted]

[redacted]

(b) Please implement the HR estimates from the Flatiron comparison for RET fusion-positive patients in the economic model, even though they were considered not useful.

In response to this question, a scenario has been provided for pralsetinib vs. best available therapy in the untreated and pre-treated populations. This scenario has been provided in the latest version of the economic model ('ID3875_Pralsetinib for *RET* fusion-positive advanced NSCLC_CEM_ACIC CQs'). In both scenarios, pralsetinib can be considered a cost-effective treatment option against best available therapy with results comparable to those presented in the base case analysis. However, given the small sample sizes used to generate clinical efficacy estimates in the best available therapy arm ([redacted]), results should be interpreted with caution.

Untreated population

The indirect treatment comparison for pralsetinib vs. best available therapy (Document B, Section B.2.9.2, page 66) used the restricted efficacy population from ARROW. To ensure that the clinical efficacy data from the indirect treatment comparison aligned with the clinical efficacy data used to inform pralsetinib OS, PFS and TTD in the economic model, the indirect treatment comparison in Document B, Section B.2.9.2 was redone using the ARROW unrestricted efficacy population (OS HR [redacted], 95% CI [redacted]; PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]).

For costs, in the Flatiron *RET* fusion-positive dataset, best available therapy ([redacted]) consisted of pembrolizumab + chemotherapy ([redacted]), platinum-based chemotherapy ([redacted]), immunotherapy monotherapy ([redacted]) and other ([redacted]). Acquisition costs were calculated from a blended mix of the reported best available therapies. Table 27 displays the calculation of acquisition costs for best available therapy. For simplicity, non-acquisition costs in the scenario (administration costs, health state costs, adverse event costs etc.) were assumed to be equal to pembrolizumab + pemetrexed + chemotherapy which represented the modal value in the Flatiron *RET* fusion-positive dataset for best available therapy.

Table 27: Best available therapy acquisition cost calculation

Flatiron *RET* fusion-positive dataset treatment	Flatiron *RET* fusion-positive dataset treatment distribution	Economic model treatment	Economic model treatment distribution to represent best available therapy	Acquisition cost per month (£)
Pembrolizumab + chemotherapy	[redacted]	Pembrolizumab + pemetrexed + chemotherapy	[redacted]	9,677
Platinum-based chemotherapy	[redacted]	Platinum-based chemotherapy	[redacted]	1,292
Immunotherapy monotherapy	[redacted]	Pembrolizumab monotherapy	[redacted]	7,624
Other	[redacted]	--	[redacted]	--
Total cost per month for best available therapy				**8,186**

Results for the scenario estimating pralsetinib vs. best available therapy in the untreated setting are presented in Table 28.

Table 28: Base-case untreated results (with PAS for pralsetinib) for pralsetinib vs. best available therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best available therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Pre-treated population

An indirect treatment comparison was conducted in the pre-treated population comparing the clinical efficacy of pralsetinib (using the unrestricted efficacy population) against best available therapy in the Flatiron dataset ([redacted]) (OS HR [redacted], 95% CI [redacted]; PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]).

For costs, it was conservatively assumed that the costs of best available therapy in the pre-treated population were represented by docetaxel monotherapy in the economic model. This represents the lowest acquisition cost per month in the economic model (£21.34 per month).

Results for the scenario estimating pralsetinib vs. best available therapy in the pre-treated setting are presented in Table 29.

Table 29: Base-case pre-treated results (with PAS for pralsetinib) for pralsetinib vs. best available therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best available therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

(c) Please explain why in the pre-treated population, the Time to Treatment Discontinuation (TTD) hazard rate was imputed by copying the PFS hazard rate. Please explain the underlying rationale and any assumptions made.

For the indirect comparisons against docetaxel monotherapy, docetaxel + nintedanib and platinum-based chemotherapy, comparator data was modelled using efficacy data from the literature (11-13). TTD was not reported for comparators in these studies. Therefore the HR for TTD for pralsetinib against these comparators is unknown. TTD is considered the most accurate endpoint to estimate treatment costs. In the absence of data, an assumption was made to assume the HR for TTD for pralsetinib against these comparators would be identical to the respective PFS HRs. This assumption implies an identical relationship between pralsetinib and comparator's TTD as is observed in the relationship between pralsetinib and comparator's PFS.

As the relationship between TTD and PFS for comparators is unknown, the directional impact of this assumption on comparator treatment costs is unknown. In the pre-treated pralsetinib arm of ARROW, TTD is comparable to PFS. Therefore, by applying the comparator PFS HR to the TTD arm of ARROW, the assumption implies that the unknown comparator TTD is comparable to comparable PFS. In oncology indications where treatments are advised to be administered until disease progression, PFS often closely resemble TTD. Where there is an absence of TTD data, a common approach in NICE appraisals is to assume PFS as a proxy for TTD. It is of note that where both comparator TTD and PFS were available for the Flatiron real world-evidence analysis in the untreated population, the HR between pralsetinib and comparators PFS closely resembled the HR between pralsetinib and comparators TTD (Document B, Section B.2.9.6, Table 24, page 92).

In the current analysis, an alternative assumption using PFS instead of TTD to model treatment costs could have been adopted to address this (as outlined in the scenario analysis, (Document B, Section B.3.8.3, Table 84, page 194). This approach would have had the advantage that PFS would be used in both treatment arms which would be consistent.

However, pralsetinib treatment costs are a key driver of model results. To model these accurately was seen as the priority for this appraisal. Therefore, the approach was taken to use the most accurate method available to model pralsetinib treatment costs.

Comparator treatment costs represent a small proportion of the incremental differences in costs between pralsetinib and comparators (Table 30). Therefore the impact of any potential deviation on the relationship between PFS and TTD for pralsetinib vs. comparators is likely to have a minimal impact on ICERs. Further, the percentages estimated in Table 30 are likely to be an overestimate in some instances since the confidential PASs for nintedanib and pemetrexed are not considered in this analysis.

Table 30: Impact of pre-treated base case docetaxel + nintedanib and platinum-based chemotherapy treatment costs on total incremental costs vs. pralsetinib

Treatment regimen	Treatment costs	Total costs	Inc. total costs vs pralsetinib	Comparator treatment costs as % of total incremental costs
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

(d) Regarding the choice for proportional hazards regression models to *"estimate hazard ratios between the pralsetinib and comparator arms"* (Section B.2.9.5, page 82), please explain whether the proportional hazards assumption was reasonable in the current context. What evidence is there to assume that the assumption is not violated?

Flatiron real-world evidence comparison (Document B, Section B.2.9.5, pages 80-91)

For the Flatiron real-world evidence efficacy analysis for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy, there is no evidence to suggest the proportional hazards assumption is violated for the OS, PFS or TTD endpoints. In each case, the Schoenfeld tests fail to be rejected at the 5% level of test and the log-negative-log plots demonstrate largely parallel curves across the observed data.

Table 31: Pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy Schoenfeld tests for proportional hazards

Treatment regimen	Schoenfeld p value
OS	[redacted]
PFS	[redacted]
TTD	[redacted]

OS, Overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation
Note: **Bold**** denotes significance at 5% level of test

Figure 3: Log-negative-log plot for the comparison with pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy

For the Flatiron real-world evidence efficacy analysis for pralsetinib vs. pembrolizumab monotherapy, there is no evidence to suggest the proportional hazards assumption is violated for the OS or TTD endpoints. In each case, the Schoenfeld tests fail to be rejected at the 5% level of test and the log-negative-log plots demonstrate largely parallel curves across the observed data. For PFS, the Schoenfeld test is significant at the 5% level of test, however, the log-negative-log plot appears to demonstrate largely parallel curves across the observed data with a narrowing of curves towards the end of the observed data where the number of events are low. Therefore, there is not considered sufficient evidence to reject the proportional hazards assumption.

Table 32: Pralsetinib vs. pembrolizumab monotherapy Schoenfeld tests for proportional hazards

Treatment regimen	Schoenfeld p value
OS	[redacted]
PFS	[redacted]
TTD	[redacted]

OS, Overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation
Note: **Bold**** denotes significance at 5% level of test

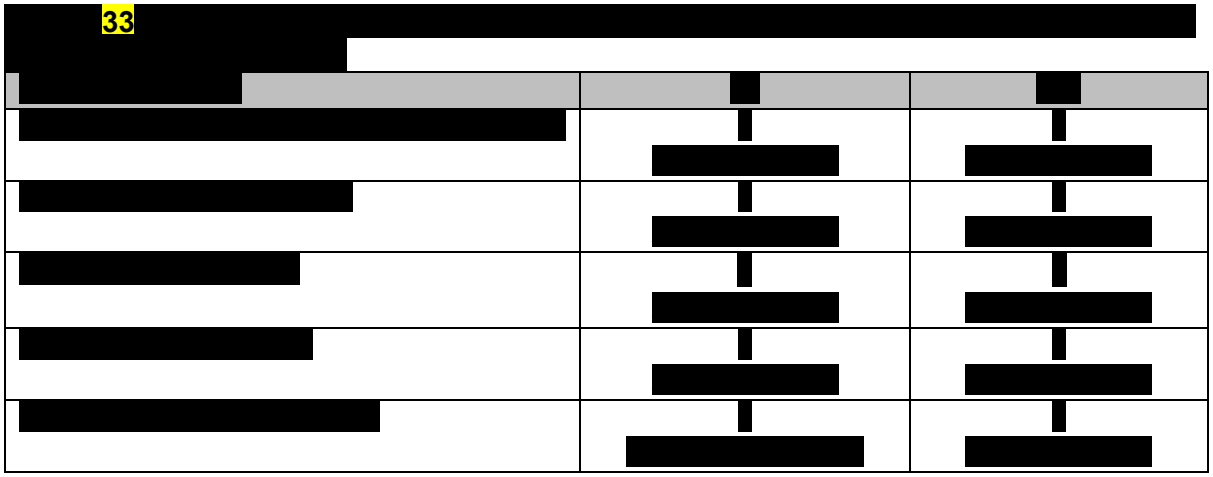
Figure 4: Log-negative-log plot for the comparison with pralsetinib vs. pembrolizumab monotherapy

WT SLR comparison (Document B, Section B.2.9.5, pages 67-80)

An assessment of the proportional hazards assumption was conducted by exploring Schoenfeld residuals and calculating a corresponding test statistic and p-value to identify whether there appears to be a statistically significant deviation away from the proportional hazards assumption. The test for proportional hazards is based on a Chi-squared test to detect whether the regression coefficient (treatment arm) varies with time.

Out of the ten comparisons conducted across OS and PFS outcomes, only one resulted in a statistically significant p-value (xxxxxx33) (ARROW vs GOIRC 02-2006 + NVALT7 for OS). For the one statistically significant p-value, the result was marginal at the 5% level of test (p-value = [redacted]). The Schoenfeld residual plot did not demonstrate a severe non-linear relationship. Therefore, it can be considered there is insufficient evidence to reject proportional hazards.

Overall, it can be assumed that for the purposes of these analyses, HR estimates are a reasonable measure of comparative efficacy.



OS, Overall survival; PFS, progression-free survival; SLR, systematic literature review; WT, wild type
Note: **Bold**** denotes significance at 5% level of test

C5. Since the ARROW study data are immature, the tails of the Kaplan-Meier (KM) curves are based on largely censored data.

Please provide, for all figures that show the visual fit of parametric survival curves alongside the observational KM curves (i.e., Figures 33, 37, 41, 45, 50, and 55), the confidence intervals surrounding the observational KM curve for proper visual assessment of fit.

Figure 5: Parametric extrapolations to model untreated OS for pralsetinib- Updated from Document B, Section B.3.3.1.1, Figure 33, page 119

LCI, lower confidence interval; OS, overall survival; UCI, upper confidence interval

Figure 6: Parametric extrapolations to model untreated PFS for pralsetinib- Updated from Document B, Section B.3.3.1.2, Figure 37, page 125

LCI, lower confidence interval; PFS, progression-free survival; UCI, upper confidence interval

Figure 7: Parametric extrapolations to model untreated TTD for pralsetinib- Updated from Document B, Section B.3.3.1.3, Figure 41, page 129

LCI, lower confidence interval; TTD, time to treatment discontinuation; UCI, upper confidence interval

Figure 8: Parametric extrapolations to model pre-treated OS for pralsetinib- Updated from Document B, Section B.3.3.2.1, Figure 45, page 134

LCI, lower confidence interval; OS, overall survival; UCI, upper confidence interval

Figure 9: Parametric extrapolations to model pre-treated PFS for pralsetinib- Updated from Document B, Section B.3.3.2.2, Figure 50, page 140

LCI, lower confidence interval; PFS, progression-free survival; UCI, upper confidence interval

Figure 10: Parametric extrapolations to model pre-treated TTD for pralsetinib- Updated from Document B, Section B.3.3.2.3, Figure 55, page 145

LCI, lower confidence interval; TTD, time to treatment discontinuation; UCI, upper confidence interval

C6. The exponential distribution is discussed in the text as one of the main distributions of interest. Yet, it does not show up in various graphs (e.g., Figures 37 and 41), possibly due to overlap with other distributions.

Please ensure that the distributions of interest (discussed in the corresponding text or with best fit or mentioned by clinical experts) are prioritized by providing updated figures/graphs in which these are clearly visible.

All Figures have been updated in the response to question C5. To avoid overcrowding of the figures, the gamma distribution has been removed from the analysis. The gamma distribution is nested within the generalised gamma distribution which has been included in the analysis. The gamma distribution does not comprise one of the six distributions recommended for survival analysis (32) and is rarely selected as a distribution in NICE appraisals.

Adverse Events

C7. For the adverse events (AEs) included in the model, the ARROW safety population was used, which was not exclusive to NSCLC and included participants on all doses. Also, AEs were assumed to be equal for the untreated and pre-treated populations.

(a) Please comment on potential differences in AEs occurring between the ARROW safety population and the target population for this appraisal.

Pralsetinib was found to be well tolerated with a predictable and manageable safety profile in both the overall safety population and in patients with *RET* fusion–positive NSCLC treated with 400 mg QD. Similar proportions of patients experienced serious adverse events (54.5% in the overall safety population and 59.1% in the *RET* fusion-positive NSCLC population), ≥Grade 3 treatment-related AEs (55.1% vs 55.2%) and deaths due to AEs (12.5% in both populations).

In the overall safety population, the most common AEs (reported in >25% of patients) were aspartate aminotransferase (AST) increased (46.0%), followed by anaemia (45.6%), constipation (41.9%), alanine aminotransferase (ALT) increased (33.9%), hypertension (32.6%), diarrhoea (29.4%), white blood cell (WBC) count decreased (26.9%), and pyrexia (25.2%).

In the *RET* fusion–positive NSCLC population, the most common AEs (reported in >25% of patients) were anaemia (45.9%), followed by increased AST (44.8%), constipation (42.0%), hypertension (34.2%), ALT increased (32.7%), neutrophil count decreased (28.8), pyrexia (25.6%) and white blood cell count decreased (25.6%).

Overall, there were no significant differences between the safety and tolerability profiles of pralsetinib in the overall safety and *RET* fusion-positive NSCLC populations.

(b) Please comment on the rationale for assuming AEs to be equal in untreated and pre-treated populations.

Adverse events were not a driver of economic model results. In the pralsetinib arm, adverse event costs represent [redacted] of total costs in the untreated setting and [redacted] of total costs in the pre-treated setting. The absolute value of the disutility decrement represents [redacted] of total QALYs in the untreated setting and [redacted] of total QALYs in the pre-treated setting. Therefore the potential impact of this assumption on base case results is likely to be negligible.

(c) Please provide AE data stratified by pre-treatment status of patients.

A summary of adverse events startified by pre-treatment status is provided below.

Table 34: Summary of AEs (overall safety population and patients with NSCLC treated at 400 mg QD)

Parameter, n (%)	Prior systemic treatment [redacted]	No prior systemic treatment [redacted]	Overall (All tumour types) n=528	*RET* fusion-positive NSCLC n=281
Any AE	[redacted]	[redacted]	525 (99.4)	279 (99.3)
≥Grade 3	[redacted]	[redacted]	406 (76.9)	212 (75.4)
TRAEs	[redacted]	[redacted]	493 (93.4)	264 (94.0)
≥Grade 3	[redacted]	[redacted]	296 (56.1)	155 (55.2)
SAE	[redacted]	[redacted]	288 (54.5)	166 (59.1)
≥Grade 3	[redacted]	[redacted]	251 (47.5)	137 (48.8)
Related SAEs	[redacted]	[redacted]	111 (21.0)	70 (24.9)
Deaths due to AEs	[redacted]	[redacted]	71 (13.4)	38 (13.5)
Deaths related to pralsetinib	[redacted]	[redacted]	6 (1.1)	2 (<1)

AE, adverse event; MedDRA, Medical Directory for Regulatory Activities; N, number of patients; NSCLC, non-small cell lung cancer; QD, once daily; SAE, serious adverse event; TRAE, treatment-related adverse event.

Health-Related Quality of Life (HRQOL)

C8. Priority question. The health state utility for the progression free state in the untreated population is quite close to the general population utility, while for the pre-treated it is significantly lower.

(a) Please justify why health state utility for the pre-treated population would be substantially lower than health state utility for the untreated population. Please provide clinical expert opinion to explain this.

The PF health state utility value used for the untreated population is 0.794. This utility value was taken from a previous NICE appraisal for EGFR mutation-positive advanced NSCLC which, given the lack of available robust evidence, represents the most comparable patient population available to the current appraisal (14). EORTC QLQ-C30 was collected in the FLAURA trial and mapped to EQ-5D values to estimate health state utilities. Similar to the *RET* fusion-positive population in the current appraisal, EGFR represents a patient population that is younger and more likely to have never smoked than the typical advanced NSCLC population. This health state utility value was approved for use by the committee in the appraisal and deemed representative of the utility of EGFR advanced NSCLC patients.

The PF health state utility value used for the pre-treated population is 0.713. This utility value was taken from a previous NICE appraisal in advanced pre-treated NSCLC and was also used in the recent selpercatinib appraisal (15, 16). EQ-5D data was taken from the first 12

weeks after randomisation from CheckMate 057 to estimate health state utilities. This health state utility value was approved by the committee in TA713 and, more pertinently, in the recent selpercatinib appraisal in *RET* fusion-positive advanced NSCLC. It was deemed representative of the utility of *RET* fusion-positive advanced NSCLC patients.

Mean (undiscounted) PFS in the economic model in the untreated setting was estimated to be 11.4-23.m. As patients progress and disease worsens, patients are expected to demonstrate deteriorating HRQoL. This was observed in the FLAURA study where in the PF health state (n=486), a health state of 0.794 was estimated and for the PD health state (n=241), a health state of 0.704 was estimated (31).

It should be noted that the modelled PD health state utility value from the FLAURA trial (0.704) and the utility value deemed acceptable by the committee in the appraisal (0.678) were both lower than the PF health state utility in the pre-treated population in this appraisal (0.713). This maintains internal consistency as whilst the majority (61-69%) of the healthier patients are modelled to go on to receive subsequent treatment (identical to the pre-treated PF health state) a minority of lower HRQoL patients will go straight to best supportive care. These patients are expected to have worse HRQoL than those who go on to receive further treatment.

(b) Please justify why the health state utility for progression free in the untreated population would be close to utility in the general population (i.e., 0.794 for population in the model compared with 0.83 for the general population using the Ara and Brazier approach mentioned in Document B), especially since the condition is considered to be end-of-life as claimed in Table 34 of Document B. Again, please provide clinical expert opinion to confirm.

RET fusion-positive patients are generally younger, more likely to have been non-smokers and fitter and healthier than WT NSCLC patients. These characteristics are associated with improved HRQoL compared to WT SLR patients. Health state utility values were taken from the FLAURA study which represents an EGFR advance NSCLC population. Patient characteristics of EGFR advanced NSCLC subjects in the FLAURA study are comparable to patient characteristics of untreated *RET* fusion-positive advanced NSCLC subjects in ARROW (median age 64.0 vs. 63.0; never smoked 64% vs. 55%).

[redacted] Similarly, in the selpercatinib NICE appraisal, a mapping analysis was

conducted in order to map EORTC QLQ-C30 data collected in LIBRETTO-001 to health state utilities in a PF *RET* fusion-positive population with a utility estimated that was substantially higher than general population utility (0.99-0.9984) (16). However, authors commented this lacked clinical plausibility.

A range of health state utility values were explored in the scenario analysis and results were demonstrated to not be sensitive to the utility vales used (Document B, Section B.3.8.3, Table 84, page 194).

The impact of the impact of age and sex-related disutility have been considered in the economic model with disutilities decreasing as patients in the model age (Document B, Section B.3.4.5, pages 155-6). This also ensures that modelled utility values always reduced to remain below the general population utility at any given age modelled.

C9. Priority question. Related to question C10, the ERG is interested in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC-QLQ-C30) data stratified for pre-treated and untreated populations to underpin the substantial utility difference between these populations as implemented in the economic model.

Please provide the EORTC data or a summary of the (unmapped and mapped) results, for the two populations separately.

[redacted]

[redacted]

[redacted]

35 [redacted]

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

[redacted]

11 [redacted]

12 [redacted]

13 [redacted]

[redacted]

14 [redacted]

C10. In Table 57 of Document B, it appears that for many (almost half) of the AEs no disutility is applied in the model because of assumption or because no data are available.

Please provide a scenario in which the missing disutilities are assumed to be equal to the disutility of fatigue, i.e., -0.074 and 23.8 days.

This scenario has been provided in the latest version of the economic model ('ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CEM_ACIC CQs').

Table 36: Scenario for assumption of adverse event utility equal to fatigue base-case untreated results (with PAS for pralsetinib)

Pralsetinib vs.	Base case ICER (£/ QALY)	Scenario ICER (£/ QALY)
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 37: Scenario for assumption of adverse event utility equal to fatigue base-case pre-treated results (with PAS for pralsetinib)

Pralsetinib vs.	Base case ICER (£/ QALY)	Scenario ICER (£/ QALY)
Docetaxel monotherapy	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Costs

C11. Priority question. Subsequent treatments for the pre-treated population are not included in the model since these are said to mainly consist of best supportive care (BSC).

(a) **Please justify the exclusion of subsequent treatments in the pre-treated population since this is not in line with the ongoing selpercatinib appraisal (ID3743), which has been referred to in the CS.**

There is not anticipated to be a substantial difference in the difference of subsequent treatments (and therefore costs) received following pralsetinib and comparators. Given marginal incremental differences between treatment arms, for simplicity, subsequent treatments were not included in the analysis. Table 38 displays the total cost of subsequent treatments following treatment with a *RET* inhibitor estimated as per the selpercatinib appraisal (ID3743) (16).

Table 38: Subsequent treatments following pre-treated

Subsequent treatment	Mean cost of subsequent treatment (£)	Patients treated with proportion following pralsetinib	Patients treated with proportion following comparator treatment
Docetaxel	765	14.9%	0.0%
Carboplatin	1,216	8.7%	25.0%
Gemcitabine	2,926	7.7%	7.7%
Erlotinib	4,136	5.5%	5.5%
Pemetrexed	8,976	4.9%	0.0%
Vinorelbine	3,947	5.1%	5.1%
Radiotherapy	7,718	55.0%	56.6%
Total (£)		**5,558**	**5,326**

(b) **Please provide a scenario, or option in the model, including subsequent treatments for the pre-treated population.**

This scenario has been provided in the latest version of the economic model ('ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CEM_ACIC CQs'). Given the minimal marginal incremental differences in costs and the impact of discounting, the exclusion of subsequent treatment costs is a conservative assumption. However, the impact on results is minimal.

Table 39: Scenario for assumption of inclusion of pre-treated subsequent treatment costs base-case pre-treated results (with PAS for pralsetinib)

Pralsetinib vs.	Base case ICER (£/ QALY)	Scenario ICER (£/ QALY)
Docetaxel monotherapy	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

C12. In the ongoing selpercatinib appraisal (ID3743), which has been referred to in the CS, monitoring costs were included in the economic model.

Please justify the choice for excluding monitoring costs (as per Table 36 of Document B: Features of the economic analysis).

Monitoring costs in the selpercatinib appraisal are identical across all treatment arms and represent, for patients in the PF health state, the cost of one oncologist visit every 3 weeks (16). In the current appraisal for pralsetinib, oncologist visits were accounted for within supportive care costs at a rate of 0.75 per month in the PF health state and 1 per month in the PD health state. These costs were approved for use by the committee in the entrectinib appraisal (TA643), which represents an appraisal in advanced NSCLC in a comparable indication. The incremental difference in costs between the two approaches is minimal (27).

Cost-effectiveness results

C13. In the untreated population in the model, there is a marked difference between the deterministic and probabilistic results, which seems to arise from the fact that in the probabilistic analysis, life years (LYs) for pralsetinib are lower, while for the comparators the LYs are higher.

Please provide an explanation for this difference.

The issue identified in clarification C15 was addressed but it did not appear to substantially impact the PSA results. At this stage it is not clear what the explanation for this difference is. Roche will continue to investigate this and seek to provide a response to NICE and the ERG when possible.

C14. Please clarify the exclusion of many parameters in the deterministic sensitivity analysis (DSA) and provide a DSA whereby all parameters are included with a tornado diagram including the top 10 most influential parameters.

Following discussion with NICE and the ERG at the Clarification Call (7th September 2021), it was agreed that the key missing parameters of interest were the curve extrapolation choices. Therefore Table 40-Table 42 display the impact on model results for each comparator where the curve extrapolation choice for each endpoint is varied.

Table 40: Impact on ICERs for pralsetinib vs. untreated and pre-treated comparators of varying OS curve extrapolation choices

	Pralsetinib vs. untreated comparators		Pralsetinib vs. pre-treated comparators		
	Pembro + chemo	**Pembro mono**	**Doce mono**	**Doce + nin**	**PBC +/- pem**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; OS, overall survival; PBC, platinum-based chemotherapy
*Denotes base case analysis

Table 41: Impact on ICERs for pralsetinib vs. untreated and pre-treated comparators of varying PFS curve extrapolation choices

	Pralsetinib vs. untreated comparators		Pralsetinib vs. pre-treated comparators		
	Pembro + chemo	Pembro mono	Doce mono	Doce + nin	PBC +/- pem
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PFS, progression free survival; PBC, platinum-based chemotherapy
*Denotes base case analysis

Table 42: Impact on ICERs for pralsetinib vs. untreated and pre-treated comparators of varying TTD curve extrapolation choices

	Pralsetinib vs. untreated comparators		Pralsetinib vs. pre-treated comparators		
	Pembro + chemo	Pembro mono	Doce mono	Doce + nin	PBC +/- pem
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; TTD, Time to discontinuation; PBC, platinum-based chemotherapy
*Denotes base case analysis

Model file

C15. PRIORITY QUESTION: Due to model design choices, Progression Free Survival (PFS) may exceed Overall Survival (OS) in individual simulations of the probabilistic sensitivity analysis (PSA). Currently, this implies that Progressed Disease (PD) state time, costs, and (quality adjusted) life years can be negative in the model. The ERG

considers this to be a potential cause for the difference between deterministic and probabilistic ICER.

Please update the model to ensure that such unrealistic model variations are not included in any model outputs. Also, please facilitate the recording of individual simulation outcomes from the PSA.

Formulas have been updated in the latest version of the economic model ('ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CEM_ACIC CQs') to ensure that both PFS and TTD do not exceed OS.

Individual simulations of PSA iterations can be found on the 'PSA_Simulations' sheet in the model.

C16. Please correct the following errors in the model:

(a) The scenario section (under results) in the model is not accessible and clicking the relevant buttons does nothing.

Hyperlinks to the scenario analysis have been included in the latest version of the economic model ('ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CEM_ACIC CQs').

(b) The "Assumptions", "Abbreviations", "References", and "PI" buttons result in an error upon interaction.

All these buttons have been removed in the latest version of the economic model ('ID3875_Pralsetinib for RET fusion-positive advanced NSCLC_CEM_ACIC CQs'). Assumptions are outlined in Document B, Section B.3.6.2, Table 72, page 170. Abbreviations are outlined at the start of Document B. References can be found in the associated sections of Document B with pdfs provided in the submission reference pack.

C17. The Probabilistic Sensitivity Analysis (PSA) analysis has a long runtime.

Please try to optimize the macro for more reasonable run times.

Roche investigated the feasibility of optimising the PSA macro in order to reduce the runtime of the PSA. Unfortunately, no solutions were able to be found to make the code more efficient and to reduce the run time.

The model contains two cost-effectiveness analyses with two treatment arms and five active comparators across the untreated and pre-treated setting. Further, PSA iterations did not converge at 1,000 iterations and therefore 5,000 iterations were conducted in order to ensure convergence.

A recent running of the PSA macro was conducted with 1,000 iterations run in 15 minutes 23 seconds.

Section D: Textual clarification and additional points

Ongoing research

D1. According to Section B.2.11 of Document B, the AcceleRET Lung trial was initiated in June 2020.

Please provide further information about this trial, including when first results can be expected.

AcceleRET is an international, randomised, open-label, Phase 3 study designed to evaluate whether the potent and selective *RET* inhibitor, pralsetinib, improves outcomes when compared to a platinum chemotherapy-based regimen chosen by the Investigator from a list of standard of care treatments, as measured primarily by progression free survival (PFS), for participants with RET fusion-positive metastatic NSCLC who have not previously received systemic anticancer therapy for metastatic disease. Participants who have centrally confirmed progressive disease on the control arm have the option to crossover to pralsetinib. The estimated enrolment is 226 patients, with 6 participating UK sites.

Primary results are expected in [redacted]

References

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Patient organisation submission

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID 3875]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	As a result of the COVID pandemic, our contact with patients and carers has largely become virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. RET alterations are found in about 1% to 2% of patients with NSCLC. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is likely that, though a younger, fitter patient group (fewer co-morbidities), RET fusion positive patients may well be diagnosed later, as they do not fit the 'typical' lung cancer patient profile. .
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some patients with Non Small Cell Lung Cancer – Target Therapies and Immunotherapies. There is, however, a need to identify further new targets and therapies for these groups. At date of writing, there are currently no NICE recommended treatments, specifically for RET fusion positive lung cancer patients. However, we understand that a decision on the Selpercatinib STA [ID3743], is imminent. Should it be made recommended, this would be the new standard. The current systemic treatment , however, would be with standard NSCLC treatment – a combination of chemotherapy and immunotherapy.
8. Is there an unmet need for patients with this condition?	yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As above, Pralsetinib will be the second therapy available specifically targeted at RET fusion positive lung cancer. The multicentre ARROW study shows this therapy has a 57% overall response rate in RET positive NSCLC patients previously treated with chemotherapy (80% of responding patients had response lasting six months or more) and 70% in those who received it as first line therapy (58% of responding patients had responses lasting for six months or more). We are not aware of any direct comparisons of Pralsetinib with Selpercatinib. Pralsetinib is a once daily oral preparation. In this time of COVID, oral therapy has clear advantage over hospital requiring, intra-venous treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. We note the most common side effects reported included anaemia, increased liver enzymes, neutropenia, constipation, musculoskeletal pain, fatigue, leukopenia and hypertension.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	As an oral therapy for a highly selected patient group, during these times of COVID, reducing hospital attendance for systemic therapy would be preferable.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Currently, would be the first targeted therapy being assessed for RET positive lung cancer, unless Selpercatinib is recommended.
- Oral therapy.
- With limited data at present, perhaps consider availability trough the Cancer Drugs Fund.
-
-

Thank you for your time.

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Professional organisation submission

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**BTOG (British Thoracic Oncology Group)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK.** **The vision of BTOG is to support and educate thoracic oncology healthcare professionals, creating a professional community to exchange ideas, information and innovation and to foster the development of research. The overall aim is to represent the needs of people with thoracic malignancies in the UK and ensure they have equitable access to optimal care.** **BTOG does not receive any funding from the NHS but is supported through sponsorship and education grants from industry and registration fees.**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**No**

manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**To reduce burden of disease and therefore improve symptoms, maintain or improve quality of life, and prolong survival. This is a palliative, not a curative, treatment.**
7. What do you consider a clinically significant treatment response? (For example, a	**Reduction in tumour size by 30% or more as determined by cross-sectional imaging.** **Or**

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**Reduction in metabolic activity (SUVmax) of an FDG-avid malignant lesion on PET scan by 30% or more.** **Or** **Statistically significant improvement in symptoms as documented on a recognised lung cancer specific, or general oncology, Quality of Life scale**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**Yes.** **RET-fusion positive lung cancer is a distinct sub-type, usually affecting those who have never smoked, and who are younger. RET-fusion lung cancer responds very well to RET tyrosine kinase inhibitors (TKIs). Access to such targeted therapies is therefore essential.** **Currently no RET TKIs have been approved by NICE or are available via the Cancer Drugs Fund (CDF) or Early Access to Medicine Scheme (EAMS). Consequently none are available for routine clinical use.**
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	**RET fusion non-small cell lung cancer (NSCLC) is nearly always of adenocarcinoma sub-type, and the license for Pralsetinib is in patients with advanced stage disease. Data supporting the use of Pralsetinib (ARROW trial: Gainor et al., Lancet Oncology (2021); 22(7):959-969) includes both treatment naïve and platinum pre-treated patients.** **Consequently the current NHS treatment paradigm would follow NICE guidelines:** **1st Line:** **Pembrolizumab, Pemetrexed and Carboplatin.** **Or** **Pemetrexed and Carboplatin.**

	Although single agent Pembrolizumab is an option for PD-L1 >50% adenocarcinoma, this is usually much less effective in patients with oncogene driven NSCLC, such as RET fusions, and so it would be an inferior choice to those above. **2nd Line:** **Docetaxel, with or without Nintedanib.** **Single agent immunotherapy (Pembrolizumab, Nivolumab or Atezolizumab) is an alternative for those who have not received immunotherapy in their 1st line regimen, however this is usually much less effective in patients with oncogene driven NSCLC, such as RET fusions, and so it would again be an inferior choice to those above.**
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**There are no NHS guidelines specific to RET-fusion NSCLC.** **RET has not yet been included in European Society of Clinical Oncology clinical guidelines.**
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**Optimal management of advanced RET-fusion NSCLC is not clearly defined.** **There is evidence for benefit of RET TKIs in both 1st line and relapsed settings, and it is not clear which – if either – is superior to the other. There are two principal RET specific TKIs in this area – Pralsetinib and Selpercatinib – but no head to head data to support one over the other.** **Therefore, although there is consensus that patients with RET-fusion NSCLC should be treated with a RET TKI, which agent, and in which line of therapy, is likely to vary between healthcare professionals.**

• What impact would the technology have on the current pathway of care?	**The technology would be an additional line of therapy, giving patients more options, and more lines of treatment.**
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**No.** **Pralsetinib is an oral anti-cancer therapy whereas all other treatments are intravenous (IV). Pralsetinib would not require chemotherapy unit time or space.** **The treatment intent (palliative) remains unchanged.**
• How does healthcare resource use differ between the technology and current care?	**Pralsetinib is an oral therapy: therefore there no requirement for chemotherapy day unit space or time.** **Each cycle lasts 28 days, whereas chemotherapy (current standard of care) is given on a 21-day cycle basis. Consequently patients on Pralsetinib would require fewer oncology clinic appointments, fewer blood tests, and would make fewer demands on the time of oncology doctors and nurses during their treatment.**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**Specialist oncology outpatient clinics.**
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**None. The routine use of oral TKIs in lung cancer is well established.**

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**Yes.** **The most recent data from the ARROW trial, an update presented at the ASCO Annual Congress in 2021(Curigliano et al., J Clin Oncol 39(15S) :9089-9089), showed the following:** **In RET+ patients who were treatment naïve, the Response Rate (RR) to Pralsetinib was 72%, Disease Control Rate (DCR) was 93%, and median Progression Free Survival was 13.0 months. Although this was not a head-to-head study, cross-trial comparison with what in the UK is likely to be the standard of care (Pembrolizumab, Pemetrexed, Carboplatin: KEYNOTE-189 trial) show a response rate of 47.6%, DCR = 84.6% and median PFS = 9.0 months (Rodriguez-Abreu et al., ASCO Annual Congress 2020). Consequently in these measures, Pralsetinib is superior to current Standard of Care.** **When used in the 2nd line (relapsed) setting, Pralsetinib demonstrated RR = 62%, DCR = 91% and median PFS = 16.5 months. This time the comparator would adenocarcinoma patients who received Docetaxel and Nintedanib in the LUME-Lung-1 trial (Reck et al., Lancet Oncology 2014). Here, the RR = 4.7%, DCR = 54% and median PFS = 3.4 months. Again, Pralsetinib is superior to the current standard of care.**
• Do you expect the technology to increase length of life more than current care?	**Yes.** **Although Overall Survival data is not yet available, the magnitude of median PFS benefit over standard of care is such that it is likely to lead to an Overall Survival benefit in the real world setting. This is especially evident when looking at the 2nd line cohort from the ARROW trial, which demonstrates the activity of this Pralsetinib compared to the very limited activity of standard Docetaxel-based chemotherapy.** **The current Phase 3 trial, AcceleRET, (which compares first-line Pralsetinib to platinum-based chemo/immunotherapy), might be expected to show an Overall Survival benefit when it finally releases it data. However, even if Praletinib is increasing survival, this may not be shown in AcceleRET because the primary end-point is median PFS, and cross-over from chemotherapy to Pralsetinib in event of progression is permitted within the trial design.**

• Do you expect the technology to increase health-related quality of life more than current care?	**Yes.** **Although formal, comparative, Quality of Life data has not been published, Pralsetinib has been to have a favourable side-effect profile. In ARROW, common grade 3 or worse treatment-related adverse events were neutropenia (18%), hypertension (11%), and anaemia (24 [10%). There were no treatment-related deaths in this population. Current chemotherapy / chemoimmunotherapy combinations have a worse side effect profile than this.** **The combination of greater efficacy, longer duration of activity, and more favourable profile is highly likely to result in improved Qualitty of Life compared to standard of care, for patients receiving Pralsetinib.**
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**Pralsetinib (with respect to this Appraisal) is only suitable for patients with advanced lung cancer and a proven RET-fusion.**
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	**From the healthcare professional perspective, Pralsetinib, which is oral, will be easier to use the current standard of care, which are intra-venous. There is less demand on chemotherapy units, and associated services. No additional requirements are needed in order to provide Pralsetinib, with lung oncology services being very familiar with oral anti-cancer drugs.** **From the patient perspective, the drug will be easier to take (fewer side effects, oral) and more convenient (long treatment cycles, no need for day-case attendance for treatment).**

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**Treatment would only be used in those who have a proven RET-fusion. This is a rare lung cancer subtype, reflecting around 1-2% of all lung adenocarcinomas. RET fusion testing is already included in the 2020/2021 National Genomics Testing Directory, and so no additional testing is required.** **Treatment would continue so long as there is clinical benefit (as assessed by radiological response and symptomatic benefit), or until unacceptable toxicity develops.**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**No.**

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	**Yes.** **This is a novel, RET-specific targeted drug, and as such is innovative.** **Please see section 14 for comments of Quality of Life.**
• Is the technology a 'step-change' in the management of the condition?	**Yes. No current RET-specific drugs are available. Early attempts at targeting RET used drugs which were no specific for RET, and so were troubled by reduced efficacy and significant toxicity. Both Pralsetinib and Selpercatinib are step-changes in the management of RET+ lung cancer.** **Targeting driver mutations in lung cancer (EGFR, ALK, ROS1) has been conclusively shown to be the optimal management strategy.**
• Does the use of the technology address any particular unmet need of the patient population?	**Yes. There is no RET-specific drug available on the NHS for the treatment of RET+ lung cancer.**
17. How do any side effects or adverse effects of the technology affect the	**Please see comments in Section 14.**

management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	**Yes. Beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice**
• If not, how could the results be extrapolated to the UK setting?	**N/A**
• What, in your view, are the most important outcomes, and were they measured in the trials?	**Response Rate (yes)** **Duration of Response (yes)** **Progression Free Survival (yes)** **Overall Survival (data not available yet)** **Safety (yes)**
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**The use of median Progression Free Survival has long been used as a surrogate for Overall Survival. The use here is in keeping with that approach, and is affected by the same advantages and limitations as other studies where PFS is (so far) the only survival data available.**
• Are there any adverse effects that were not	**No.**

apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No.**
20. How do data on real-world experience compare with the trial data?	**There is no significant real-world data experience yet published to compare with trial data.**
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	**No.**
21b. Consider whether these issues are different from issues with current care and why.	**N/A.**

Key messages
22. In up to 5 bullet points, please summarise the key messages of your submission. • **RET-fusion lung cancer is rare, and usually affects younger patient who are non-smokers.** • **Pralsetinib is a novel RET-specific targeting drug. No other such agents are available.** • **In Phase 2 trials, Pralsetinib has shown impressive efficacy in the 1st and relapsed setting, but Overall Survival data is not yet available.** • **The activity of Pralsetinib is greater than that which we see with chemotherapy in comparative settings.** • **Pralsetinib has a favourable side effect profile, better than that which we see with chemotherapy, and is easier to take and to administer.**

Thank you for your time.

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Pralsetinib for RET fusion-positive advanced non-small cell lung cancer [ID3875]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, United Kingdom (UK) in collaboration with Groningen University Medical Centre, the Netherlands

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Declared competing interests of the authors

None.

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Contributions of authors

Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Thea van Asselt acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Charlotte Ahmadu, Steef Konings, Maarten Postma, Mohammed al Khayat and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Pawel Posadzki and Susan O'Meara 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 and Jos Kleijnen 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

ADR	Adverse drug reaction
AE	Adverse events
AIC	Akaike Information Criteria
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BIC	Bayesian Information Criteria
BID	Twice daily
BMI	Body mass index
BOR	Best overall response
BRAF	B-raf (mutation)
CCDC6	Coiled-Coil Domain Containing protein 6
CCOD	Clinical cut-off date
C1D1	Cycle 1 day 1
CBR	Clinical benefit rate
CD137	Cluster of differentiation 137
CI	Confidence Interval
CL	Clarification letter
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTLA4	Cytotoxic-T-lymphocyte-associated antigen 4
DCIS	Ductal carcinoma in situ
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group Performance Score
EDM	Enhanced Data Mart
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
ERG	Evidence Review Group
ESS	Effective sample size
FE	Fixing errors
FIH	First-in-human
FV	Fixing violations
GG	Generalised gamma
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IDP	Individual patient data
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
IV	Intravenous
KIF5B	Kinesin Family Member 5B
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
MAIC	Match-adjusted indirect comparison
MDP	Measurable disease population

MeSH	Medical subject headings
MJ	Matters of judgement
MTC	Medullary thyroid carcinoma
MTD	Maximum tolerated dose
n	Number of patients treated
NA	Not applicable
NE	Not evaluable
NSCLC	Non-small cell lung cancer
NCOA4	Nuclear Receptor Coactivator 4
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSW	Propensity score weighting
QALY	Quality adjusted life year
QD	Once daily
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
QTcF	QT-interval of the 12-lead electrocardiogram corrected for heart rate by Fridericia's formula
RANO	Response assessment in neuro-oncology
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
ROS1	c-ros oncogene 1
RP2D	Recommended Phase 2 dose
RR	Response rate
SAE	Serious adverse events
SD	Stable disease
SLR	Systematic literature review
SMD	Standardised mean difference
SoC	Standard of care
STA	Single technology appraisal
TTD	Time to treatment discontinuation
TTOD	Time to off treatment
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cells
WHO	World Health Organization
WT	Wild type
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 Review Group (ERG) as being potentially important for decision making. Where possible, it also includes the ERG'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 relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report in Sections 2, 3, 4, 5, 6 and 7.

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

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

Issue no.	Summary of issue	Report Sections
1	The appraisal population is restricted to non-squamous non-small cell lung cancer (NSCLC), whereas the population defined in the final National Institute for Health and Care Excellence (NICE) scope includes all patients with NSCLC.	2
2	The comparators are not in line with the final NICE scope, leaving the relative benefits of pralsetinib unclear.	2 and 3.2
3	A main trial upon which the conclusions are based (the ARROW trial) has only 13 United Kingdom (UK) patients potentially limiting generalisability to UK setting.	3.2
4	The systematic literature reviews (SLRs) upon which the estimations were based suffered from methodological problems hindering the Evidence Review Group's (ERG's) ability to draw robust conclusions about pralseltinib's safety and effectiveness.	3.1
5	There are no safety data for pralsetinib vs. comparators listed in the NICE final scope making it impossible to draw firm conclusions regarding the relative safety and tolerability of pralsetinib.	3.3
6	P Propensity score weighting (PSW) analysis, instead of only a naïve comparison, could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed. This would have allowed adjustment for confounding.	3.3
7	No correction for crossing curves in probabilistic sensitivity analysis (PSA). Overall survival (OS) could therefore fall below progression free survival (PFS) in individual simulations of the PSA, leading to negative post progression survival.	4.2.2
8	Constant benefit of pralsetinib assumed without justification and based on immature data. The company submission (CS) did not discuss treatment waning, nor was it included in the economic model.	4.2.6

Issue no.	Summary of issue	Report Sections
9	There is substantial uncertainty in survival curve extrapolations due to immaturity of data.	4.2.6
10	Adverse event incidences included in the model were potentially subject to error. The incidences for AEs for pralsetinib and comparators could not always be reproduced based on the sources provided in the CS.	4.2.7
11	There is a lack of direct evidence to inform health-related quality of life (HRQoL). The utility scores from previous appraisals that were used to inform the model may not be valid for the population in this decision problem.	4.2.8
AEs = adverse events; CS = company submission; ERG = Evidence Review Group; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression free survival; PSA = probabilistic sensitivity analysis; SLRs = systematic literature reviews; UK = United Kingdom		

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the correction to prevent for crossing curves and the implementation of a treatment waning effect. In a scenario, the ERG explored alternative hazard ratios to account for substantial uncertainty surrounding these. In general, changing the company assumptions would increase the ICER of pralsetinib relative to the comparator treatments.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival (OS)) and quality of life 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:

- Increasing progression free survival (PFS) and overall survival (OS).

Overall, the technology is modelled to affect costs by:

- A higher monthly cost of treatment, compared to the majority of comparator treatments
- Its oral administration, instead of intravenous (IV) administration for comparator treatments
- A higher proportion of patients receiving subsequent treatment after first line, compared to comparator treatments

The modelling assumptions that have the greatest effect on the ICER are:

- For the untreated population
    - The hazard ratios for time to treatment discontinuation (TTD) and OS
    - Limiting the time horizon to 5 years
    - The method used to model treatment duration
- For the pre-treated population
    - The hazard ratio for OS
    - The utility for progressed disease

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

The decision problem addressed in the company's submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on squamous NSCLC patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1. The appraisal population is restricted to those with non-squamous NSCLC cell lung cancer which limits generalisability to patients with squamous NSCLC

Report Section	**2**
Description of issue and why the ERG has identified it as important	The population defined in the scope is: People with advanced rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy. The population in the CS is limited to patients with non-squamous NSCLC.[1] Studies in this narrower population may not generalise to the wider population specified in the final NICE scope.
What alternative approach has the ERG suggested?	The ERG recommends that Table 3 of Document B be modified to state that the evidence in the company submission is restricted to patients with non-squamous NSCLC.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Additional study with the population specified in the final NICE scope.
CS = company submission; ERG = Evidence Review Group; NSCLC = non-small cell lung cancer; RET = rearranged during transfection	

Table 1.3: Key issue 2. Exclusion of potentially relevant comparators listed in the NICE scope

Report Section	**3.2**
Description of issue and why the ERG has identified it as important	Numerous comparators listed in the NICE final scope were omitted from the CS, including: - for untreated patients: pembrolizumab monotherapy, pembrolizumab with carboplatin and paclitaxel, atezolizumab monotherapy, nivolumab plus ipilimumab, chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin), pembrolizumab with carboplatin and paclitaxel, and nivolumab plus ipilimumab - for treated patients: atezolizumab monotherapy, pembrolizumab monotherapy, docetaxel, and best supportive care. The NICE clinical expert did not agree with some of these omissions, and the ERG noted that a complete justification for omission of best supportive care was missing.
What alternative approach has the ERG suggested?	The ERG has no suggestions for an alternative approach.
What is the expected effect on the cost effectiveness estimates?	Uncertain.

Report Section	3.2
What additional evidence or analyses might help to resolve this key issue?	A randomised trial or network meta-analysis with the comparators listed in the NICE scope.
CS = company submission, ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence	

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

The ERG identified three major concerns with the evidence presented on the clinical effectiveness. These were: there were few UK patients in the ARROW trial, limiting relevance to a UK National Health Service (NHS) setting (Table 1.4), the systematic literature reviews (SLRs) suffered from methodological problems limiting the ERG's ability to draw conclusions from them (Table 1.5), and lack of comparative safety data (Table 1.6).

Table 1.4: Key issue 3. Questionable generalisability to UK population

Report Section	3.2
Description of issue and why the ERG has identified it as important	A main trial upon which the conclusions are based (the ARROW trial) has only 13 UK patients [2] This may limit generalisability to the UK.
What alternative approach has the ERG suggested?	Due to the small number of patients in the UK, no alternative approach is possible until more UK data become available
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	A randomised trial with a higher proportion of patients based in the UK.
ERG = Evidence Review Group; UK = United Kingdom	

Table 1.5: Key issue 4. Methodological problems with systematic literature reviews

Report Section	3.2
Description of issue and why the ERG has identified it as important	The SLRs upon which the estimations were based suffered from methodological problems including inconsistency of response rate definitions, lack of dual independent data extraction, exclusion of non-randomised studies, and lack of comprehensive quality assessment of included studies. This hindered the ERG's ability to draw robust conclusions about the safety and effectiveness of pralsetinib.
What alternative approach has the ERG suggested?	No alternative approach is possible at this time.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	An updated SLR that closely follows standard methodological guidance such as the Cochrane Handbook.
ERG = Evidence Review Group; SLRs = systematic literature reviews; UK = United Kingdom	

Table 1.6: Key issue 5. Lack of comparative safety data

Report Section	**3.3**
Description of issue and why the ERG has identified it as important	There are no comparative safety data for pralsetinib vs. comparators listed in the NICE final scope for the treatment of patients with advanced, unresectable, RET-altered NSCLC, due to available evidence being a single arm study. This makes it impossible to draw firm conclusions regarding the relative safety and tolerability of pralsetinib.
What alternative approach has the ERG suggested?	Provide best available comparative safety data.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Comparative analysis of safety of pralsetinib and other comparators listed in the final NICE scope.
ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; RET = rearranged during transfection	

Table 1.7: Key issue 6. Propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed

Report Section	**3.3**
Description of issue and why the ERG has identified it as important	A naïve comparison using GOIRC 02-2006 + NVALT was used to inform the comparison with platinum-based chemotherapy +/- pemetrexed. This means that there was no adjustment for confounding. However, in the Flatiron study, a source of data to conduct PSW analysis for other comparisons, this regimen was used in more patients than both pembrolizumab plus pemetrexed plus chemotherapy and pembrolizumab monotherapy (16.1% vs. 14.1% and 7.6%).
What alternative approach has the ERG suggested?	Flatiron could have been used for the comparison with platinum-based chemotherapy +/- pemetrexed.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Flatiron could be used for the comparison with platinum-based chemotherapy +/- pemetrexed.
ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PSW = propensity score weighting; RET = rearranged during transfection	

1.5 The cost effectiveness evidence: summary of the ERG'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 ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.8: Key issue 7. No correction for crossing curves in probabilistic sensitivity analysis

Report Section	**4.2.2**
Description of issue and why the ERG has identified it as important	In the PSA of the company model, the OS curve could cross the PFS and TTD curves, which led to negative post-progression survival in a proportion of the simulations.
What alternative approach has the ERG suggested?	The ERG corrected this in the ERG preferred assumptions model and added additional diagnostics to be able to detect the problem in the company model.
What is the expected effect on the cost effectiveness estimates?	The correction increased the probabilistic ICER but there was no impact on the deterministic ICER.
What additional evidence or analyses might help to resolve this key issue?	Issue is resolved.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; TTD = time to treatment discontinuation	

Table 1.9: Key issue 8. Constant benefit of pralsetinib assumed without justification and based on immature data

Report Section	**4.2.6**
Description of issue and why the ERG has identified it as important	The benefit of pralsetinib was assumed to be constant over time, even though the evidence from ARROW was insufficient to justify this. Any other justification for excluding treatment waning was also lacking.
What alternative approach has the ERG suggested?	Given the median follow-up time in ARROW (just over a year overall, 9.5 months for untreated population), the ERG suggests implementing treatment waning starting at 2 years over a period of 3 years. This was varied in a scenario.
What is the expected effect on the cost effectiveness estimates?	The ICER will increase.
What additional evidence or analyses might help to resolve this key issue?	Mature data from a comparative study.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

Table 1.10: Key issue 9. Substantial uncertainty in survival curve extrapolations due to immaturity of data

Report Section	**4.2.6**
Description of issue and why the ERG has	Because of small sample size and immaturity of data, in particular in the untreated population, the estimated hazard ratios and the survival curve extrapolations are surrounded by substantial uncertainty.

identified it as important	
What alternative approach has the ERG suggested?	Because of difficulty in choosing the appropriate distributions for the curve, the ERG prefers to calibrate the hazard ratios so that both pralsetinib and comparator curves are best aligned with the expert estimates. The ERG implemented this approach in a scenario.
What is the expected effect on the cost effectiveness estimates?	As the calibrated hazard ratios favour the comparators, the ICERs will increase.
What additional evidence or analyses might help to resolve this key issue?	Mature data from a comparative study
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

Table 1.11: Key issue 10. Adverse event incidences included in the model potentially subject to error

Report Section	**4.2.7**
Description of issue and why the ERG has identified it as important	Adverse event incidences as included in the model seem subject to inconsistencies and potentially errors. This goes for both the pralsetinib and comparators arms.
What alternative approach has the ERG suggested?	As the ERG could not verify which incidences were the correct ones for pralsetinib, no alternative approach was suggested.
What is the expected effect on the cost effectiveness estimates?	Minor. Changing the AE incidences of the four AEs in Table 4.7 to the higher rates from the n=528 population only very slightly increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Clarification on AE rates for both pralsetinib and comparators is needed.
AEs = adverse events; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

Table 1.12: Key issue 11. Lack of direct evidence to inform health-related quality of life

Report Section	**4.2.8**
Description of issue and why the ERG has identified it as important	Mapped utilities from the ARROW study were disqualified by the company and instead, utility values from previous appraisals were used to inform the economic model. These were however not specific to the RET fusion-positive population and the difference in utility scores between the untreated and pre-treated population was not reflected in the mapped EORTC QLQ-C30 data.
What alternative approach has the ERG suggested?	No alternative approach as the ERG is unsure what the correct approach would be given lack of data.

Report Section	4.2.8
What is the expected effect on the cost effectiveness estimates?	Uncertain, but sensitivity and scenario analyses suggest that the impact on the ICER is limited.
What additional evidence or analyses might help to resolve this key issue?	Direct evidence on HRQoL in a RET fusion-positive population, both untreated and pre-treated.
EORTC = European Organisation for Research and Treatment of Cancer; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QLQ-C30 = quality of life questionnaire; RET = rearranged during transfection	

1.7 Summary of the ERG's view

In conclusion, cost effectiveness estimates of pralsetinib in the first line are subject to considerable uncertainty, mainly because of immaturity of data, small sample size, and lack of comparative evidence in various areas. The ERG considers the clinical evidence presented to be not sufficiently robust to inform the economic model. Even when all the ERG preferred assumptions were implemented in the model, uncertainty remained on a number of issues, such as the appropriateness of the hazard ratios and the methods and data used to derive them, long-term efficacy of pralsetinib, and comparative HRQoL values. In the second line these uncertainties are present as well, but the ICERs for the second line comparisons are well outside the cost-effective range, and therefore the uncertainty has less of an impact on decision making (see Tables 1.12 and 1.13).

Table 1.13: Deterministic and probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic CS base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic CS base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Fixing errors: Correction for crossing curves in PSA (probabilistic ICERs)					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Fixing errors: Cisplatin dosage in the 2L is changed to 75 mg (effect only Platinum-based chemotherapy 2L)					
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Matter of judgement: Treatment waning OS, assuming start waning at 2 years over a period of 3 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER, incremental cost effectiveness ratio; OS = overall survival; QALYs, quality-adjusted life years

Table 1.14: Deterministic scenario analyses (conditional on ERG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 1: Treatment waning OS, assuming time till waning 1 years over 2 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 2: Calibrated hazard ratios for comparators at 3 years for OS and PFS untreated and pre-treated populations					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 3: TTD = PFS (for all TTD curves (except treatment cut-off))					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 4: Relative dose intensity = 90% for all treatments					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER, incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALYs, quality-adjusted life years; TTD = time to treatment discontinuation

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 (CS)	Rationale if different from the final NICE scope	ERG comment
Population	People with advanced RET fusion-positive NSCLC who require systemic therapy.	Patients with advanced, unresectable, *RET*-altered non-squamous NSCLC, MTC, and other *RET*-altered solid tumours	In their response to clarification, the company stated: "The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced NSCLC. The non-squamous histology patients represent 95.8% of patients in the ARROW study and is the population of most interest in this appraisal…In addition, very small numbers of patients with squamous NSCLC were enrolled in the LIBRETTO-001 (selpercatinib) trial and Roche did not present any evidence on using selpercatinib in this tumour histology. [redacted]	The rationale provided by the company does not amount to evidence that the population studied in the company submission is applicable to patients with squamous NSCLC.

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
			[redacted]; therefore, Table 3 has not been updated to reflect a narrower population." [3]	
Intervention	Pralsetinib	Pralsetinib	N/A	The intervention is in line with the NICE scope
Comparator(s)	**Untreated disease:** For people with non-squamous NSCLC whose tumours express programmed death-ligand 1 (PD-L1) with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab monotherapy (subject to ongoing appraisal ID1678)	Several comparators listed in the final NICE scope were omitted. **For untreated patients**, the following comparators were omitted: pembrolizumab monotherapy, pembrolizumab with carboplatin and paclitaxel, atezolizumab monotherapy, nivolumab plus ipilimumab, chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin), pembrolizumab	From response to clarification letter: "A high proportion of *RET* fusion-positive patients are non-squamous (1.4% of patients enrolled in ARROW were squamous NSCLC). Due to the low incidence of *RET* fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore, this appraisal is concentrated solely on non-squamous NSCLC patients.	The comparators are not in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
	• Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) 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) or with or without pemetrexed maintenance treatment • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	with carboplatin and paclitaxel, and nivolumab plus ipilimumab **For treated patients with squamous NSCLC PD-L1 <50%**, the following comparators were omitted: atezolizumab monotherapy, pembrolizumab monotherapy, docetaxel, and best supportive care. **For treated patients with squamous NSCLC PD-L1 >50%,** the following comparators were omitted: gemcitabine with carboplatin or cisplatin, vinorelbine with carboplatin or cisplatin, docetaxel, and best supportive care.	[redacted]	

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
	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) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683)			

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
	• Atezolizumab monotherapy (subject to ongoing appraisal ID1678) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)			

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
	For previously treated disease: For people with RET fusion-positive NSCLC: • Selpercatinib (subject to ongoing appraisal ID3743) For people with non-squamous NSCLC PD-L1 ≥50%: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care For people with non-squamous NSCLC PD-L1 50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel			

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
Outcomes	The outcome measures to be considered include: • OS • PFS • response rate • TTD • adverse effects of treatment • HRQoL	As per scope with one exception: HRQoL was not reported in the clinical effectiveness section of the CS. In their response to clarification, the company provided mapped utilities based on the EORTC QLQ-C30 scores, but these were nor used to inform the economic model. QALYs in the economic model were based on utilities in previous NICE appraisals.	The company stated that the HRQoL data was not viewed as being sufficiently robust enough to inform decision making.	The ERG believes that HRQoL should be included in the main analyses.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.			The approach taken for the economic analysis is largely in line with the reference case. No fully incremental analysis was performed though, see Table 4.3. The costs associated with diagnostic testing for RET-fusion mutation was not included in the company base-case because standard genomic testing in advanced NSCLC in the NHS was thought to be imminent. The company performed a scenario including costs of genomic testing.

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
	Costs will be 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. The availability of any managed access arrangement for the intervention will be taken into account. The use of pralsetinib in NSCLC is conditional on the presence of RET gene fusion. The economic modelling should include the costs associated with diagnostic testing for RET in people with advanced NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 5.9 of the Guide to the Methods of Technology Appraisals.			

	Final scope issued by NICE	Decision problem addressed in the company submission (CS)	Rationale if different from the final NICE scope	ERG comment
Subgroups to be considered	If evidence allows subgroup analysis by • Previous therapy The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The following subgroups have been considered in the clinical section of this submission: • ORR by *RET* genotype and prior anticancer therapy.	N/A	Economic model included both the untreated (first line) and the pre-treated (second line) population, results reported separately.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A	N/A

Based on Table 3 and pages 10 to 12 of the CS.[1]

CS = company submission; EORTC = European Organisation for Research and Treatment of Cancer; ERG = Evidence Review Group; HRQoL = health-related quality of life; MTC = medullary thyroid carcinoma; N/A = not applicable; NSCLC = non-small cell lung cancer; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; OS = overall survival; ORR = objective response rate; PFS = progression free survival; PD-L1 = programmed death-ligand 1; PSS = Personal Social Services; QALY = quality adjusted life year; QLQ-C30 = Quality of Life Questionnaire; RET = rearranged during transfection; TTD = time to treatment discontinuation

2.1 Population

The population defined in the scope is: people with advanced RET fusion-positive NSCLC who require systemic therapy.[5] The population in the CS is limited to patients with non-squamous NSCLC.[1] Only 1.4% of patients enrolled in the only source of evidence for pralsetinib, the ARROW trial, were squamous NSCLC. Indeed the company stated: "*Due to the low incidence of RET fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore this appraisal is concentrated solely on non-squamous NSCLC patients,…"* (p.14, CS)[1]

The ERG therefore recommended in the clarification letter that Table 3 (specifying the population in the decision problem) should be updated to reflect this narrower population. In their response to the clarification questions, the company stated several reasons for this and did not update Table 3. The main rationales in the response to clarification questions and the ERG response are listed below.

1. The company stated that *"the marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced NSCLC"*.[3] The ERG does not believe that this addresses our point, which is that the analyses and studies included in the CS do not apply to patients with squamous NSCLC.
2. The company stated that *"the non-squamous histology patients represent 95.8% of patients in the ARROW study and is the population of most interest in this appraisal; however, Roche believes the appraisal population should be all encompassing including squamous patients (in line with the expected licence) rather than restricted to non-squamous, as per the selpercatinib appraisal"*.[3] The majority of ARROW patients having non-squamous NSCLC is a large part of the reason that the ERG believes that the evidence presented by the company does not necessarily apply to the population specified in the final NICE scope, which includes patients with squamous NSCLC.[5]
3. The company stated that [redacted] despite the fact that: *"very small numbers of patients with squamous NSCLC were enrolled in the LIBRETTO-001 (selpercatinib) trial and [the company responsible for selpercatinib] Eli Lilly did not present any evidence on using selpercatinib in this tumour histology"*. [3] The ERG believes that while the [redacted] appraisal may share a number of similarities with this one, that each appraisal must be taken on its own merits, so appeal to the [redacted] cannot be assumed to have direct relevance to this one.

A NICE clinical expert noted that *"the company is making the assumption that RET fusions are so rare in S NSCLC that only the NS NSCLC pathway needs to be considered. From the TA point of view I think this is reasonable as it makes things simpler (NHSE will allow use of pralsetinib in patients with RET fusion S NSCLC in any case if the current indication is recommended)"*.[6]

ERG comment: The decision problem addressed in the CS is narrower than that specified in the final scope, which is does not specify that the population should consist exclusively of patents with non-squamous NSCLC. The extent to which the evidence presented by the company applies to patients with squamous NSCLC is unclear. While patients with squamous NSCLC represent a minority of patients with NSCLC, the ERG believes that it is nonetheless important to know whether the evidence applies to this population.

2.2 Intervention

The intervention (pralsetinib) is in line with the scope.

Pralsetinib is administered as a once-daily oral dose by the patients themselves, or their caregivers, at home or in an ambulatory setting.[7] Oral administration alleviates the burden associated with the traditional use of non-targeted intravenous (IV) chemotherapy. For instance, patient preference for oral therapy is largely associated with the reduced need for hospital admissions due to lengthy treatment schedules with IV chemotherapy and the reduced frequency of clinical visits,[8] which is critical given that clinical experts confirmed to Roche that chemotherapy units in UK clinical practice are in crisis due to severe capacity constraints.[9] Additional benefits of oral therapy, versus IV treatment, include alleviation of healthcare resource use and the requirement for hospital beds.[10, 11] Oral therapy can also eliminate the risk of infusion-related adverse reactions that are common with cancer treatment, [12] while providing patients more freedom to remain active.

2.3 Comparators

The NICE final scope describes a series of comparators, stratified according to untreated disease/previously treated disease, tumour histology and biomarker status as outlined in Table 2.2 below.

Table 2.2: Comparators listed in NICE scope

For untreated disease:	For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab monotherapy (subject to ongoing appraisal ID1678) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)
	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) o with or without pemetrexed maintenance treatment • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)
	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) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment
	For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Atezolizumab monotherapy (subject to ongoing appraisal ID1678) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)

	For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)
For previously treated disease:	For people with RET fusion-positive NSCLC: Selpercatinib (subject to ongoing appraisal ID3743)
	For people with non-squamous NSCLC PD-L1 ≥50%: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care
	For people with non-squamous NSCLC PD-L1 50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel
NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; RET = Rearranged during transfection	

By contrast, the company uses a smaller set of comparators for the appraisal (Tables 1 & 2 and pages 15-6 of Document B in the CS. Specifically, several untreated comparators in the ITC are missing i.e., nivolumab plus ipilimumab, atezolizumab monotherapy, atezolizumab plus bevacizumab plus carboplatin plus paclitaxel, or docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with carboplatin or cisplatin with or without pemetrexed maintenance. This was based on clinical experts' opinion.

In their response to the clarification questions, the company listed all of the comparators that were excluded in their analysis, together with a rationale (Tables 15 and 16 of the clarification response).[3] The company justification includes the statement that *"A high proportion of RET fusion-positive patients are non-squamous (1.4% of patients enrolled in ARROW were squamous NSCLC). Due to the low incidence of RET fusion-positive squamous patients and the small number of squamous patients in ARROW, it was not deemed suitable or feasible to include this population; therefore, this appraisal is concentrated solely on non-squamous NSCLC patients.* [redacted]

However, the company did not present any evidence on using selpercatinib in this tumour histology. The ERG believes that while the [redacted] appraisal may share a number of similarities with this one, that each appraisal must be evaluated on its own merits, and therefore appeal to the [redacted] cannot be assumed to have direct relevance to this one.

National Institute for Health and Care Excellence clinical experts made several comments on the company's choice of comparators.[6] The experts agreed that: for pralsetinib 2L, nivolumab and pembrolizumab could be omitted as meaningful comparators for 2L pralsetinib.

However, the experts also recommended that a number of comparators included in the final NICE scope (but not the CS) should have been included. This includes a recommendation to include atezolizumab as a comparator for 1L pralsetinib. Related to 2L pralsetinib, the expert also noted that *"[t]he company things that maint[enance] pemetrexed only follows cisplatin+pemetrexed. This is wrong: maint[enance] pemetrexed follows carboplatin+pemetrexed as well."*[6]

The ERG notes that the NICE clinical expert did not comment on the exclusion of best supportive care as a comparator.

ERG comment:

The ERG does not understand the rationale for the company's exclusion of a number of comparators listed in the final NICE scope.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- OS
- PFS
- response rate
- TTD
- adverse effects of treatment
- HRQoL

These outcomes were all assessed in the ARROW trial.

2.5 Other relevant factors

According to the company, pralsetinib satisfies an "unmet need for targeted treatment among *RET* fusion-positive NSCLC patients and the benefits that earlier targeted treatment would offer to these patients."[2] Pralsetinib is designed to selectively target oncogenic RET alterations and RET-activating mutations, including primary RET fusions and mutations that cause cancer and secondary RET mutations that could drive resistance to treatment.

This appraisal does not fulfil the end-of-life criteria setting as specified by NICE because although the life expectancy of patients eligible for pralsetinib is normally less than 24 months in both the untreated and pre-treated populations, there is insufficient evidence that pralsetinib offers an extension to life of at least 3 months compared with current NHS treatment (see Section 7 below).

According to the company, there are no known equality issues relating to the use of pralsetinib in patients with RET fusion-positive advanced NSCLC (CS, Section B.1.1.1).

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a SLR to assess the efficacy and safety of treatment for people with locally advanced or metastatic RET-positive NSCLC. A more specific aim was to compare pralsetinib with relevant comparators used in clinical practice. Initially, the company planned to use the SLR to underpin a matching adjusted indirect comparison (MAIC) of pralsetinib versus comparators of interest. However, it emerged that it was not feasible to conduct MAICs for all relevant comparators when restricting inclusion of studies to those recruiting participants with *RET*+ NSCLC. To address the gaps in evidence relating to the comparators of interest, the company performed a second SLR that modified the participant eligibility criteria to include people with wild-type (WT) NSCLC. Wild type tumours are those without a genetic mutation or rearrangement or that have unknown mutation status. The aim of the second SLR was to identify randomised controlled trials (RCTs) that evaluated relevant comparator interventions in participants with WT advanced or metastatic NSCLC.

Section 3.1 critiques the methods of both SLRs including search methods, study eligibility criteria, data extraction, assessment of methodological quality and methods of evidence synthesis.

3.1.1 Searches

Appendix D of the CS provided details of the SLR searches used to identify clinical efficacy and safety evidence. The same literature searches were used to identify cost effectiveness studies (Appendix G), HRQoL studies (Appendix H), and cost and healthcare resource use studies (Appendix I). Additional SLR searches were conducted to identify RCTs of patients with WT NSCLC. Details of these searches were reported in Appendix L.

Database searches for the clinical and safety SLR were conducted in October 2020. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for clinical efficacy and safety of RET+NSCLC (October 2020)

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	Ovid	1974 to 9 October 2020	9 October 2020
	MEDLINE, MEDLINE In-Process Citations, Epub Ahead of Print & Daily Update	Ovid	1946 to 6 October 2020	9 October 2020
	EBM reviews	Ovid	-	9 October 2020
	EconLit	Ovid	1886 to 1 October 2020	9 October 2020
Conference Proceedings	ASCO	Not reported	2018-2020	Not reported
	ELCC	Not reported	2018-2020	Not reported
	ESHG	Not reported	2017-2019	Not reported
	ESMO	Not reported	2018-2020	Not reported

	ESP	Not reported	2017-2019	Not reported
	ISPOR (International and European)	Not reported	2018-2020	Not reported
	HTAi	Not reported	2017-2019	Not reported
	NCRI	Not reported	2018-2020	Not reported
	SMDM (North American and European)	Not reported	2017-2019	Not reported
	USCAP	Not reported	2018-2020	Not reported
HTA websites	NICE	http://www.nice.org.uk	Not reported	Not reported
	SMC	https://www.scottishmedicines.org.uk/	Not reported	Not reported
	PBAC	http://www.pbs.gov.au/pbs/	Not reported	Not reported
	CADTH	https://cadth.ca/	Not reported	Not reported
	HAS	https://www.has-sante.fr/	Not reported	Not reported
	IQWiG	https://www.iqwig.de/en/	Not reported	Not reported
	G-BA	https://www.g-ba.de/english/	Not reported	Not reported
	ICER	https://icer-review.org/	Not reported	Not reported
The reference lists of studies included in the SLR were reviewed to identify any further relevant publications which were not identified as part of the SLR.				
EBM reviews consists of the following resources: American College of Physicians (ACP) Journal Club; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews; Cochrane Clinical Answers; Cochrane Methodology Register; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; and National Health Service Economic Evaluation Database (NHS EED)				
ASCO = American Society of Clinical Oncology; ELCC = European Lung Cancer Conference; ESHG = European Society of Human Genetics; ESMO = European Society for Medical Oncology; ESP = European Society of Pathology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; HTAi = Health Technology Assessment International; NCRI = National Cancer Research Institute; SMDM = Society for Medical Decision Making; USCAP = United States and Canadian Academy of Pathology; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; PBAC = Pharmaceutical Benefits Advisory Committee; CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = Haute Autorité de Santé; IQWiG = Institute for Quality and Efficiency in Health Care; G-BA = Federal Joint Committee; ICER = Institute for Clinical and Economic Review				

ERG comment:

- The selection of databases searched was very comprehensive. Full details of the database searches, including the database name, host platform and date searched, were provided.
- Trials registers were not searched.
- Conference proceedings were searched. The search strategies or search terms used, date of searches, and results, were not reported in the CS. In response to the ERG clarification letter full details of the conference proceedings search strategies were provided.
- Health technology assessment organisation websites were searched, but details of the search terms used, dates of searches, and results, were not reported in the CS. Details of the search terms used were provided in response to the ERG clarification letter.
- Extensive use of truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE) were included in the search strategies. There were no language or date limits.

- As the searches consisted of the population only (RET+NSCLC), separate searches for safety data, cost effectiveness studies, health-related quality-of-life studies and costs and healthcare resource use studies, were not required.
- The search facet for RET might have benefited from the inclusion of more synonyms.
- The searches were conducted in October 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant studies published since October 2020.

As the CS SLR for RET+NSCLC did not identify evidence for some of the relevant comparators, the company conducted an additional SLR to identify RCTs examining missing relevant comparator interventions conducted in patients with WT NSCLC to inform an indirect treatment comparison with pralsetinib.[13] Details of the searches conducted for this SLR were reported in Appendix L. Database searches for this SLR were conducted in February 2021. A summary of the resources searched is provided in Table 3.2.

Table 3.2: Resources searched for clinical efficacy of WT NSCLC. February 2021.

Search strategy element	Resource	Host/Source	Date Range	Date searched
Databases	Embase	Ovid	1974 to 1 February 2021	2 February 2021
	MEDLINE, MEDLINE In-Process Citations, Epub Ahead of Print & Daily Update	Ovid	1946 to 1 February 2021	2 February 2021
	EBM reviews	Ovid	-	2 February 2021
Conference Proceedings	ASCO	Not reported	Not reported	Not reported
	ESMO	Not reported	Not reported	Not reported
	ELCC	Not reported	Not reported	Not reported
	IASLC/WCLC	Not reported	Not reported	Not reported
HTA websites	NICE	https://www.nice.org.uk/	Not reported	Not reported
	CADTH	https://cadth.ca/	Not reported	Not reported
	PABC	https://www.pbs.gov.au/pbs/	Not reported	Not reported
	ICER	https://icer-review.org/	Not reported	Not reported
The reference lists of studies included in the SLR were reviewed to identify any further relevant publications which were not identified as part of the SLR.				
EBM reviews consists of the following resources: American College of Physicians (ACP) Journal Club; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews; Cochrane Clinical Answers; Cochrane Methodology Register; Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA) database; and National Health Service Economic Evaluation Database (NHS EED)				
ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ELCC = European Lung Cancer Congress; IASLC/WCLC = International Association for the Study of Lung Cancer/World Conference on Lung Cancer; NICE = National Institute for Health and Care Excellence; CADTH = Canadian Agency for Drugs and Technologies in Health; PBAC = Pharmaceutical Benefits Advisory Committee; ICER = Institute for Clinical and Economic Review				

ERG comment:

- The selection of databases searched was good. Full details of the database searches, including the database name, host platform and date searched, were provided.
- Trials registers were not searched.
- Conference proceedings were searched. The search strategies or search terms used, date of searches, and results, were not reported in the CS. In response to the ERG clarification letter full details of the conference proceedings search strategies were provided.
- Health technology assessment organisation websites were searched, but details of the search terms used, dates of searches, and results were not reported in the CS. Details of the search terms used were provided in response to the ERG clarification letter.
- As this was an update search, the searches were limited to 2017 to 2021. There were no language limits.
- Study design search filters for RCTs were included. It would have been helpful if the search filters had been cited in the methods section, as current practice recommends.[14]
- The search facet for NSCLC was rudimentary and would have benefited from the inclusion of more synonyms.
- The search facet for drug interventions did not include all of the drug interventions listed in the NICE scope; though this SLR was conducted to identify those drug interventions unidentified in the CS SLR for RET+NSCLC.
- The search facet for drug interventions would have benefited from the inclusion of more synonyms and registry numbers.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.3.

The study eligibility criteria used in the first SLR (SLR 1, to underpin the MAICs in people with *RET*+ NSCLC) and second SLR (SLR 2, to identify comparators to pralsetinib used in people with WT NSCLC) are summarised in Tables 3.1 and 3.2 respectively.

Table 3.3: Eligibility criteria for SLR 1 (basis for MAICs in people with *RET*+ NSCLC)

Domain	Inclusion criteria	Exclusion criteria
Population	Adult patients with stage III/IV *RET*+ NSCLC as the total population or subgroup, regardless of treatment line (first, second or beyond)	None stated
Interventions	Pralsetinib	None stated
Comparators	Pharmacological interventions for NSCLC including relevant comparators used in clinical practice	None stated

Domain	Inclusion criteria	Exclusion criteria
Outcomes	Efficacy: Survival (including OS and PFS) Response rate (including ORR, DOR, CBR and DCR) and TTD Safety: Number of participants with ≥1 AE or SAE Treatment withdrawal or discontinuation (e.g., due to AEs or lack of efficacy) Common (grade 3 or 4) AEs (list of specific AEs agreed at data extraction to include the five most commonly reported AEs in the ARROW study) HRQoL	Studies were excluded if no outcome data were reported for patients treated with specific interventions; no other details of exclusion criteria were provided
Study design	Interventional clinical trials (phase I/II/III; single arm or with ≥2 arms) Extension phases of trials Prospective and retrospective observational or registry studies Cross-sectional surveys Case-control studies Prospective case series	Study protocols only Review and editorial articles Animal and in vitro studies Single-patient case reports
Geography	No restriction	None stated
Date of publication	No restriction	None stated
Language restrictions	No restriction. The primary focus was English language publications or non-English language publications with an English abstract.*	Non-English language publications**

Source: based on Section D.1, Table 5 and Figure 1 of Appendix D of the CS[15]

*verbatim from Table 5 of Appendix D;[15] **from Figure 1 of Appendix D;[15] ^from Table 20 of company's response to clarification letter;[3] ^^the company confirmed that no specific exclusion criteria were applied in their response to the clarification letter (question B19)[3]

AE = adverse event; ARROW study = Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer study; CBR = clinical benefit rate; CS = company submission; DCR = disease control rate; DOR = duration of response; HRQoL = health-related quality of life; MAIC = matching adjusted indirect comparison; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; *RET*+ = rearrangement during transfection positive; SAE = serious adverse event; SLR = systematic literature review.

Table 3.4: Eligibility criteria for SLR 2 (to identify comparators used in WT NSCLC)

Domain	Inclusion criteria	Exclusion criteria
Population	Adult patients with stage III/IV WT NSCLC, regardless of treatment line (first, second or beyond)	Paediatric patients
Interventions and comparators	Pharmacological interventions: *First line* • Pembrolizumab‡ (monotherapy or in combination with pemetrexed/platinum-based chemotherapy) • Platinum-based chemotherapy in combination with pemetrexed or paclitaxel§ *Second-line and beyond* • Docetaxel alone or combined with nintedanib • Nivolumab monotherapy • Platinum-based chemotherapy in combination with pemetrexed or paclitaxel§	• Non-pharmacological interventions (e.g., surgery, radiotherapy) • Other immunotherapies in the second-line setting (pembrolizumab, atezolizumab) • Nivolumab combination therapies • Platinum-based chemotherapy as monotherapy • Diagnostic interventions (e.g., screening)
Outcomes	**Efficacy:** • Survival (including OS and PFS) • Response rate (not specified further) • TTD **Safety:** • To include grade 3 or 4 AEs HRQoL	Outcomes not listed in the 'Inclusion criteria' column
Study design	• RCTs (phase I/II/III) • Extension phases of RCTs	• Pharmacokinetic studies • Animal and in vitro studies • Controlled clinical trials (non-RCTs, interventional, prospective) • Prospective and retrospective observational or registry studies • Cross-sectional surveys • Case-control studies • Prospective case series • Case reports • Review and editorial articles
Geography	No restriction	None stated

Domain	Inclusion criteria	Exclusion criteria
Date of publication	Studies published during 2017 and later were included. Studies published pre-2017 were of interest but were identified from re-screening relevant files associated with previous SLR 1.	Studies published pre-2017
Language restrictions	English language publications or non-English language publications with an English abstract.	Non-English language publications without an English abstract

Source: based on Section L.4, Table 40 and Figure 10 of Appendix L of the CS[16]
Footnote: ‡At project inception, the indication was line-agnostic pembrolizumab; however, it was subsequently agreed that nivolumab would be representative of targeted agents in the second line setting and therefore the inclusion criteria were restricted to first line pembrolizumab only. §Restricted to paclitaxel only; nab-paclitaxel excluded (both footnotes recorded verbatim from Table 40 of Appendix L[16]).
AE = adverse event; CS = company submission; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; SLR = systematic literature review; TTD = time to treatment discontinuation; WT = wild type.

ERG comment:

SLR 1

Specific, eligible comparators for SLR 1 are not clear from the study eligibility information in Table 5 (*"Pharmacological interventions for NSCLC"*) or Section D.1 (*"…relevant comparators used in clinical practice."*) of Appendix D.[15] Therefore, the nature of the treatment comparisons at this stage of the evidence synthesis is uncertain and it is unclear to what extent the selection of comparators reflects current practice in the UK NHS.

Discrepancies between SLR 1 and SLR 2

The ERG noted some differences between SLRs 1 and 2 in terms of study eligibility criteria.

The listed eligible outcomes for SLR 2 are not the same as those for SLR 1. SLR 2 omits response rate definitions and does not mention two of the safety outcomes from SLR 1 (the number of participants with at least one AE or SAE; and treatment withdrawal or discontinuation because of AEs or lack of efficacy). This impact of this on estimation is uncertain.

The listed eligible study designs differ between the two SLRs. A range of clinical trial, non-randomised and observational study designs were eligible for SLR 1. SLR 2 includes only phase I, II or III RCTs or extension phases of RCTs, and excludes non-randomised experimental and observational study designs. The reason for this discrepancy is not explained. The ERG note that SLR 2 is an update of an earlier review,[17] (as explained in Section L1 of Appendix L[16]). However, the eligibility criteria for study design also differ between SLR 2 and the earlier review (the earlier review included phase II, III or IV RCTs and non-RCTs, including cross-over trials).[17] The exclusion of non-randomised and observational study designs from SLR 2 is a cause for concern because of the potential omission of data on safety outcomes. The impact of this on data availability (and therefore estimation) is uncertain. In addition, it would appear that phase IV RCTs are excluded from SLRs 1 and 2 and although it may have been anticipated that such trials would not yet be available for evaluations of pralsetinib, the impact of this omission is unclear.

On the basis of tabulated information, it is not clear whether studies published before 2017 were eligible for inclusion in SLR 2 (see Table 3.2 above and Table 40 of Appendix L).[16] However, further information suggests that studies published before 2017 were eligible for inclusion but were not sought within the bibliographic database searching because this was covered by the earlier review[17] in which searches were conducted up to 2017 to identify patients undergoing all lines of treatment for WT NSCLC (see page 103 of Sections L1 and L2; and page 108 of Section L4 of Appendix L).[16] The company confirmed this within their response to the clarification letter (question B24) and went on to outline the following steps undertaken to identify relevant RCTs published before 2017 for SLR 2:[3]

- The titles and abstracts of RCTs excluded from the earlier review[17] on the basis of investigating first-line treatments were re-screened to determine whether they met the eligibility criteria for SLR 2.
- The data extraction file of the earlier review (assessing second-line and beyond RCTs)[17] was examined to identify RCTs that met the eligibility criteria for SLR 2.

In light of the overall information, the ERG considers that there are no inappropriate study eligibility restrictions on the basis of date of publication for SLR 2.

SLRs 1 and 2

Both SLRs restrict inclusion to English language publications or non-English publications with an English abstract (see Tables 3.1 and 3.2 above). In the clarification letter, the ERG asked the company to assess the impact of excluding relevant material wholly published in languages other than English for both reviews (question B22).[18] In their response, the company explained that the search strategies for both reviews allowed retrieval of all languages and the language restriction was applied during assessment of study eligibility.

For SLR 1,[15] the company excluded four reports at the title and abstract screening stage on the basis of language, [Iwama, Matej, Jin and Wang 2009 Chinese J of Lung Cancer - from p40-41 of CL response] maintaining that the titles of the papers indicated ineligibility (explained in the company's response to clarification question B22).[3] On examination of the bibliographic details (Table 3.5 below), the ERG agrees that the four reports would be unlikely to meet the review's inclusion criteria. [Iwama, Matej, Jin and Wang 2009 Chinese J of Lung Cancer - from p40-41 of CL response]. Therefore, the impact of excluding wholly non-English language reports from SLR 1 is likely to be minimal.

Table 3.5: References excluded from SLR 1 at title and abstract screening stage on the basis of non-English language

Reference
Iwama E, Takayama K, Baba E, Nakanishi Y. [Personalized medicine in non-small-cell carcinoma]. Fukuoka Igaku Zasshi. 2014 Mar;105(3):57-66. Japanese. PMID: 25000657.[19]
Matěj R, Rohan Z, Němejcová K, Dundr P. Molekulární patologie plicních karcinomů pro rutinní praxi - update 2017 [Molecular pathology of lung cancer in routine diagnostic practice: 2017 update]. Cesk Patol. 2017 Winter;53(4):159-166. Czech. PMID: 29227119.[20]
Jin LL et al. The progress of KIF5B-RET fusion gene in non-small cell lung cancer. Chinese Journal of Tuberculosis & Respiratory Diseases. 2013. 36(7):524-6.[21]
Wang J et al. Targeted therapy for advanced non-small cell lung cancer in the elderly. Chinese Journal of Lung Cancer. 2009. 12(7):821-825.[22]
Source: Company's response to the clarification letter (question B22).[3]

In the response to the clarification letter the company provided a table (Table 3.16) to show which studies from the SLR were potentially relevant and why studies were excluded from a naïve comparison or MAIC.[3]

Table 3.6: Studies considered for selection in WT SLR for each comparator

Setting	Comparator	Number of potentially relevant studies	Studies excluded	Reason for exclusion
Untreated	Pembrolizumab + pemetrexed + chemotherapy	5	3	Abstract only studies: 2; second line only studies: 1
Untreated	Pembrolizumab monotherapy	8	5	Second-line only studies: 5
Untreated	Platinum-based chemotherapy + pemetrexed or paclitaxel	68	68	Comparator not applicable for NICE appraisal
Pre-treated	Docetaxel monotherapy	44	0	--
Pre-treated	Docetaxel + nintedanib	1	0	--
Pre-treated	Nivolumab monotherapy	7	7	Comparator not applicable for NICE appraisal
Pre-treated	Platinum-based chemotherapy +/- pemetrexed	4	2	Abstract only studies: 1; non-English language studies: 1

Source: Table 22, Clarification response.[3]
NICE = National Institute for Health and Care Excellence

Continuing their response to the clarification letter (question B22), the company explained that although no references were excluded for SLR 2[16] at the title and abstract screening stage on the basis of language, two Chinese language publications were excluded following full paper review.[3] One was excluded because it did not report relevant outcome data, the primary focus being assessment of serum levels of vascular endothelial growth factor (VEGF) and endothelin and immunological function.[23] The ERG is satisfied that this is an appropriate rationale for exclusion.

The company described how the second Chinese paper[22] was considered for inclusion within the *"second-line platinum-based chemotherapy in combination with pemetrexed or paclitaxel evidence base"*.[3] The company highlighted that this trial recruited a smaller number of participants (n=110) compared with the two trials included in the pooled analysis which were selected for consideration in the meta-analysis (GOIRC 02-2006 and NVALT7; n=479)[24] and also made the point that the participants would have been predominantly Chinese, which limits the external validity of results. For these reasons, the company decided that translation of this paper into English was not required.[3] The ERG is not convinced that sample size and/or ethnicity are appropriate reasons for exclusion (ethnicity is not listed as an exclusion criterion for SLR 2) and therefore it would have been preferable to have this paper translated and include the comparator data. The impact of excluding this paper from SLR 2 is further explored in Section 3.3.

3.1.3 Critique of data extraction

3.1.3.1 SLR 1

According to information in Appendix D, relevant data for SLR 1 were extracted into a Microsoft Excel template by one reviewer. A second reviewer performed an independent check of data against the source material.[15]

The company was asked to discuss the potential biases arising from not undertaking dual, independent data extraction (question B21 in the clarification letter).[18] In their response, the company explained that the following process was undertaken by the second reviewer, claiming that this was robust and would mitigate bias:

- *"Review the publication(s) associated with the study for extraction, highlighting any relevant data for extraction."*[3]
- *"Check that all data from the publication(s) had indeed been extracted into the data extraction table (DET) in the correct cell (in this way, any data 'missed' by the first extractor was included in the Excel sheet – any additional data extracted were highlighted and checked by the first extractor [any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser])*[3]
- *"Check that the correct values had been extracted (any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser)"*[3]

Methods for resolving disagreements in data extraction between the two reviewers were not described in the CS,[15] and the clarification letter requested further detail on this (question B23).[18] The company replied that disagreements were resolved through consensus between the two reviewers where possible, and by consulting a third reviewer if necessary.[3]

In response to the clarification letter question about calculations undertaken for the MAIC (question B20),[3] the company confirmed that the calculations mentioned in Section D.1 of Appendix D[15] were not undertaken because the planned MAIC was not performed (see Section 3.1.5 below).

3.1.3.2 SLR 2

There was neither a description of data extraction methods for SLR 2 nor tabulation of extracted, eligible studies and therefore it is not possible to judge the rigour of the process.[16]

In their response to the clarification letter, the company explained that no additional calculations were necessary for SLR2: *"For the naïve treatment comparisons, no baseline characteristic data were used and so there was no need to calculate any percentages for example. Similarly, as individual patient data were used for the propensity scoring analysis, no additional calculations were required"*.[3]

ERG comment: The data extraction process for SLR 1 is not in line with recommended good practice i.e., dual, independent data extraction, particularly for outcome data.[25] The ERG does not consider that the process described by the company would sufficiently address the risk of bias or error. Considering this, the possibility of bias and error within the data extraction process cannot be discounted. This said, the approach used for resolving disagreements was satisfactory.

Because of these limitations to the methodology of SLR 2, it was not possible for the ERG to (a) assess the rigour of the data extraction process, or (b) draw any conclusions about the safety and effectiveness of pralsetinib based on SLR 2.

3.1.4 Quality assessment

3.1.4.1 SLR 1

Table 10 in Section D.3 of Appendix D (quality assessment for each trial)[15] suggests that the Downs and Black checklist for non-randomised studies[26] was used to assess the methodological quality of studies included in SLR 1 (the checklist was not referenced). The ERG notes that some included studies were not represented in Table 10 when compared Table 6 of Appendix D (publications included in the SLR). The rationale for excluding some studies from the methodological assessment table (Table 10) was not explained.[15]

The methodological quality assessment of the ARROW study was not presented with the initial CS but was provided as part of the response to clarification questions (Table 21).[3] The assessment was based on a published paper[27] and was conducted using the Downs and Black checklist (again, no reference for the checklist was provided by the company).[26]

3.1.4.21SLR 2

There was no mention of any methodological quality assessment for SLR 2.[16]

ERG comment: Details of the methodological quality process were lacking for SLR 1 (i.e., the number of reviewers involved and methods for resolving disagreements). Whilst the Downs and Black checklist is an appropriate tool for appraising the methodological quality of non-randomised studies, the incomplete presentation of tabulated information and lack of information on the process leaves the ERG uncertain about the quality of the process undertaken and means that the possibility of inaccurate and/or incomplete information cannot be discounted. The impact in terms of the degree of confidence in estimates of effect is also uncertain.

It was not possible for the ERG to judge the methodological quality of the included evidence for SLR 2 because no information was provided. The impact in terms of the degree of confidence in estimates of effect is therefore uncertain.

3.1.5 Evidence synthesis

Given the availability of only one trial of the intervention, i.e., ARROW, no head-to-head synthesis was possible. Instead, a set of indirect comparisons were performed, at least partly informed by SLR 2, as described in Section 3.3

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

3.2.1 Details of ARROW trial

The main evidence for the clinical effectiveness of pralsetinib identified in the CS was from the ARROW trial.[2] This trial (n=528) was a phase I/II, multicentre, non-randomised, multi-cohort, first-in-human (FIH) open-label study of patients with advanced, unresectable, *RET* fusion-positive NSCLC and other *RET* altered solid tumours.[28] In order to define the maximum tolerated dose (MTD), patient cohorts consisted of one to three patients for pralsetinib at 30 mg, 60 mg, and 100 mg once daily (QD) and three to six patients for higher dose levels, 200 mg, 300 mg, 400 mg, and 600 mg, as well as for the twice daily (BID) schedule. Phase I continued until the recommended Phase 2 dose (RP2D) was determined, upon which the Phase 2 expansion stage began.[2, 28]

To determine the safety, pharmacokinetics, pharmacodynamics, and anti-tumour activity of pralsetinib at the RP2D dose in patients with different types of *RET*-driven malignancies, patients were enrolled

into one to seven groups based on their disease type and/or prior therapy status (when applicable), with the exception of groups three and four where patients had to have an oncogenic *RET* fusion or mutation solid tumour.[28]

- Group 1: NSCLC with a *RET* fusion previously treated with a platinum-based chemotherapy
- Group 2: NSCLC with a *RET* fusion not previously treated with a platinum-based chemotherapy, including those who had not had any systemic therapy
- Group 3: MTC previously treated with cabozantinib and/or vandetanib
- Group 4: MTC not previously treated with cabozantinib or vandetanib
- Group 5: Other solid tumours with a *RET* fusion previously treated with standard of care appropriate for the tumour type
- Group 6: Any solid tumours with a *RET* alteration (fusion or mutation) previously treated with a selective RET tyrosine kinase inhibitor (TKI)
- Group 7: Other solid tumours with a *RET* mutation previously treated with standard of care appropriate for the tumour type

This phase consisted of a screening period up to 28 days, a 28-day cycle treatment period, an end-of-treatment (EOT) visit at least 14 ± 7 days following the last dose of study drug and a follow-up telephone contact for resolution of any AEs 30 ± 7 days after the last dose of pralsetinib, or at the time the patient initiates another antineoplastic therapy.[28] Thus, the minimum duration of patient participation was approximately 3 months.[28] After the first treatment cycle, patients could continue to receive pralsetinib until progression of disease, intolerance, or any of the other reasons for discontinuation of treatment, and a patient was considered to have completed the study if he/she had completed all required visits.[28] Patients without documented progressive disease (PD) at the time of treatment discontinuation were to be followed for PFS with tumour assessments every 3 months until documented PD or initiation of another antineoplastic therapy.[28] Patients were also asked to participate in post-treatment OS follow-up, until death or study closure. [28] The end of the study was defined as the time that the last patient completes his/her last visit, including assessments performed as part of the PFS and OS follow-up. [28]

A summary of the methodology of the ARROW Phase I/II study is presented in Table 3.7 below.

Table 3.7: Summary of the methodology of the ARROW trial

Trial design	Phase I/II, multicentre, non-randomised, open-label, single arm clinical trial
Participant eligibility criteria	Patients aged ≥18 years with unresectable *RET* fusion–positive NSCLC and other advanced solid tumours, who have consented to provide tumour tissue for *RET* status confirmation and are willing to consider an on-treatment tumour biopsy, if considered safe and medically feasible by the treating investigator
Settings and locations where the data were collected	Phase 1 was completed with 62 patients (58 from the USA, four from Europe) Phase 2 dose expansion is ongoing in 79 centres and 13 countries: Belgium, China France, Germany, Hong Kong, Italy, South Korea, the Netherlands, Singapore, Spain, Taiwan, the UK, and the USA
Trial drugs and concomitant medications	Phase I: Pralsetinib administered QD at 30 mg, 60 mg and 100 mg dose levels, BID schedules explored at dose levels ≥200 mg, then QD administration at 200 mg, 300 mg, 400 mg and 600 mg dose levels Phase II: Oral pralsetinib 400 mg QD

	Permitted concomitant medications: medications and treatments other than those specified in the CS as prohibited concomitant medications, were permitted during the study
Primary endpoint(s)	Objective response rate by RECIST v1.1 criteria by patients' disease type, and/or *RET*-altered status if applicable, and/or prior treatment status if appropriate, safety and tolerability
Other endpoints used in the economic model / specified in the scope	Secondary endpoints: duration of response, clinical benefit rate, disease control rate, PFS, OS, in all patients by disease type and/or *RET*-altered status, if applicable, and/or prior treatment status, if appropriate Exploratory endpoints: time-to-off treatment, CNS activity assessed by BICR, changes in patient-reported outcomes as assessed by the EORTC QLQ-C30 questionnaire instruments
Pre-planned subgroup analyses	ORR by *RET* genotype and prior anticancer therapy
Source: Section B.2.3.2 of the CS[28] ADR = adverse drug reaction; AE = adverse event; BID = twice-daily; BICR = blinded independent central review; CNS = central nervous system; CS = company submission; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression free survival; QD = once daily; *RET* = rearranged during transfection; UK = United Kingdom; USA = United States of America	

ERG comment(s): The ERG notes that the evidence for the efficacy and safety of pralsetinib in the population specified for this submission, is limited to one single arm study (phase II is still ongoing). No studies comparing pralsetinib to systemic treatment options or best supportive care, in advanced RET fusion-positive NSCLC who require systemic therapy, were included in the CS.

Representativeness of the UK population

ARROW Phase II is an ongoing multi-centre study (79 study centres) across 13 countries.[28] The company was asked to confirm the number of participants recruited within UK-based study sites in the ARROW trial.[18] The company stated that: '*Thirteen patients were recruited into the ARROW trial from UK-based study sites.*'[3]

As a high proportion of patients of Asian ethnicity were enrolled in the ARROW study, the company were asked to clarify how the distribution of different ethnic groups in the study would be generalisable to the UK population. The company stated that: *'clinical experts raised no concerns about the distribution of ethnicities in the enrolled population and overall they agreed that the study population reflected patients seen in UK clinical practice.'*[3]

As part of their critical appraisal of the ARROW study(Table 21, page 38 of the Clarification Response),[3] the company noted a number of potential problems with generalisability (see below) which support the ERG's view. The company used the Downs and Black checklist for assessing the methodological quality of the ARROW study.[26] Three questions that related to representativeness (below) were marked as 'unclear'.

1. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
2. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

3. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?

The company was asked to confirm the extent to which the reported 1.4% of patients with squamous cell NSCLC in the ARROW study related to the UK population. The company stated that: *'given that RET fusions are seen in 1—2% of patients with NSCLC most often in those with adenocarcinoma histology, the small proportion (1.4%) of squamous RET fusion-positive NSCLC patients enrolled in ARROW is to be expected and reflective of what would be observed in UK clinical practice.'*[3]

ERG comment: The ERG believes that the extent to which the ARROW study population is representative of UK patients with respect to demographic and disease characteristics is unclear.

3.2.2 Statistical analyses of the ARROW Phase I/IIA trial

Analysis populations in ARROW included:[28]

- Safety population: all patients who were initiated with 400 mg QD pralsetinib.
- Efficacy population: all patients with *RET* fusion–positive NSCLC in the safety population who were initiated with 400 mg pralsetinib on or prior to 22 May 2020 (primary population for efficacy analysis).
- *RET*-altered measurable disease population (MDP): all patients in the efficacy population who had measurable (target) disease per response evaluation criteria in solid tumours (RECIST) v1.1 (or response assessment in neuro-oncology (RANO), if appropriate for tumour type) at baseline according to blinded central review and sufficient evidence of a *RET* alteration.
- Unrestricted efficacy population: all patients in the safety population with *RET* fusion–positive NSCLC who were initiated with 400 mg pralsetinib regardless of date of initial dosing (used to assess time-to-event for progression-free survival and overall survival).
- Response-evaluable population: patients in the efficacy population who had measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for disease type) at baseline, and had at least one evaluable post-baseline disease response assessment performed and had no major protocol violation (used for efficacy analyses of CNS activity only).

At the data cut-off of 6 November 2020, a total of 528 patients with all tumour types received ≥1 dose of pralsetinib 400 mg QD and were included in the safety population.[28] The efficacy population consisted of 233 patients and 216 patients were included in NSCLC MDP (patients who had received 400 mg QD as starting dose in Phase I were pooled with patients in Phase II for efficacy analyses).[28]

The unrestricted efficacy population is a broader population of patients with *RET* fusion–positive NSCLC and was not defined in the ARROW clinical study protocol.[28]

The primary endpoint of the study is ORR, and analyses were based on the NSCLC MDP and efficacy population.[28] Objective response rate was defined as the proportion of patients with confirmed best overall response (BOR) of complete response (CR) or partial response (PR) for ≥2 assessments with ≥28 days and no PD in between.[28] Each patient's BOR was derived based on RECIST v1.1, and summarised by count and frequency for the CR, PR, stable disease (SD), PD or not evaluable (NE) categories.[28] The response-evaluable population was used for the primary efficacy endpoint as a sensitivity analysis for BOR.[28] Details of definitions of secondary endpoints are given in Section 3.2.5.

The hypothesis and sample size calculations were based on ORR and were specific to the response-evaluable *RET*-altered population (excluding groups 4, 6, and 7) for each Phase 2 expansion group.[28] Details of sample size justifications can be found in Section B.2.4.1 of the CS.

ERG comment: Statistical analysis appears to have been conducted appropriately.

3.2.3 Patient characteristics of the ARROW Phase I/II trial

Table 3.7 shows the baseline characteristics of patients in MDP and efficacy population in the ARROW study (the two populations stated as being used in the primary endpoint analysis). Most patients in the NSCLC MDP group were female (51.9%), <65 years of age (66.5%), and white (52.3%) or Asian (38.4%).[28] 38% had a history of/ current central nervous system (CNS) metastases, and 68.5%, 58.3%, and 38% had received prior systemic, platinum-based and radiation treatment, respectively.[28] Most participants had an Eastern Cooperative Oncology Group performance score (ECOG PS) of zero or one, with just six (2.8%) having an ECOG PS of two.[28]

The majority of patients in the efficacy population were female (52.4%), with a median (range) age of 60 (26 to 87) years of age, and predominantly white (51.9%) or Asian (39.5%).[28] 37.3% had history of current CNS metastases, and 67.8%, 58.4%, and 38.6% had received prior systemic, platinum, and radiation therapies.[28] Most participants also had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with just six (2.6%) having an ECOG PS of 2.[28]

Table 3.8: Summary of baseline characteristics of patients with *RET* fusion–positive NSCLC in the MDP and efficacy population

	Measurable Disease Population			Efficacy Population		
	All *RET* positive NSCLC n=216	**Prior Systemic Treatment n=148**	**Treatment naïve n=68**	**All *RET* positive NSCLC n=233**	**Prior Systemic Treatment n=158**	**Treatment naïve n=75**
Median age, years (range)	60.0 (26, 87)	60.0 (26, 85)	60.5 (30, 87)	60.0 (26, 87)	59.5 (26, 85)	63.0 (30, 87)
≥65, %	37.5	35.1	42.6	37.8	34.2	45.3
Sex, female, %	51.9	53.4	48.5	52.4	54.4	48.0
ECOG PS, %						
0	33.8	29.7	42.6	33.5	29.7	41.3
1	63.4	66.9	55.9	63.9	67.1	57.3
2	2.8	3.4	1.5	2.6	3.2	1.3
Histology type, %						
Adenocarcinoma	95.8	94.6	98.5	96.1	94.9	98.7
Squamous	1.4	1.4	1.5	1.3	1.3	1.3
Undifferentiated	<1.0	<1.0	0.0	<1.0	<1.0	0.0
Other	2.3	3.4	0.0	2.1	3.2	0.0
Brain metastases %	38.0	40.5	32.4	37.3	39.2	33.3
Smoking history, %						
Never	61.6	65.5	52.9	62.2	65.8	54.7
Former	34.3	31.8	39.7	33.5	31.6	37.3
Current	2.8	1.4	5.9	2.6	1.3	5.3
Unknown	1.4	1.4	1.5	1.7	1.3	2.7

	Measurable Disease Population			Efficacy Population		
	All *RET* positive NSCLC n=216	**Prior Systemic Treatment n=148**	**Treatment naïve n=68**	**All *RET* positive NSCLC n=233**	**Prior Systemic Treatment n=158**	**Treatment naïve n=75**
***RET* fusion partner, %**						
KIF5B	71.3	73.0	67.6	70.4	72.2	66.7
CCDC6	18.1	17.6	19.1	17.6	17.7	17.3
NCOA4	0.0	0.0	0.0	<1.0	0.0	1.3
Other	10.6	9.5	13.2	11.6	10.1	14.7
Prior treatment, %						
Chemotherapy	59.2	86.5	0.0	59.2	87.3	0.0
Platinum chemotherapy	58.3	85.1	0.0	58.4	86.1	0.0
PD-(L)1 inhibitors	30.6	44.6	0.0	29.6	43.7	0.0
Multikinase inhibitor(s)	18.5	27.0	0.0	18.9	27.8	0.0
Prior Radiation therapy	38.0	46.6	19.1	38.6	46.8	21.3
Prior cancer related surgeries/ procedures	47.2	50.7	39.7	49.8	51.9	45.3

Source: Table 8 of the CS[28]
CS = company submission; CCDC6 = Coiled-Coil Domain Containing protein 6; ECOG PS = Eastern Cooperative Oncology Group performance status; KIF5B = Kinesin Family Member 5B; MDP = measurable disease population; NCOA4 = Nuclear Receptor Coactivator 4; NSCLC = non-small cell lung cancer; PD-(L) 1 = programmed death-(ligand) 1; PFS = progression free survival; RET = rearranged during transfection; % = percentage

ERG comments:

- The NICE final scope defined the population of interest as those with advanced RET fusion-positive NSCLC. However, the company have restricted the appraisal population to patients with untreated non-squamous NSCLC, stating in the CS that it was due to *'...the low incidence of RET fusion-positive squamous patients*.'(page 13 of the CS)[28] This also reflects that 95.8% of patients in the ARROW study were of non-squamous histology.[3]
- In addition, although the inclusion criteria for the ARROW study specified patients with a baseline ECOG PS score of zero to one, however the company clarified that before protocol amendment 4.1, six patients (2.8%) with an ECOG PS score of 2 were enrolled into the trial and thus received pralsetinib.[3]
- The time-to-off treatment (TTOT) results used to inform the economic model were those performed in the broader unrestricted population, however the TTOT results available in the clinical study report (CSR) for the efficacy population are at a data cut-off of 18 November 2019 and are thus outdated for this submission. Justifiably, a broader population can used for time-to-event time points, however baseline and patient characteristics for this population has not been made available. Patient characteristics for the other analysis populations were also not made available in the CS.

3.2.4 Quality assessment of the ARROW Phase I/II trial

In the CS, the company stated that, *"no randomised clinical trials for pralsetinib were identified in the systematic literature review, therefore a quality assessment of the clinical effectiveness evidence was not conducted."*[28]. However, as stated in Section 3.1.4, a quality assessment based on a published paper[27] which was conducted using the Downs and Black checklist, was later provided by the company in their response to clarification questions.[3, 26] No information was provided on the number of reviewers who assessed the quality of the study and no statements were provided to support the judgements made by the company. Hence, the ERG re-assessed the study using the same quality criteria and results are shown in Table 3.9.

Table 3.9: Quality assessment for ARROW

Question	Response	
	CL response	ERG
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes
4. Are the interventions of interest clearly described?	Yes	Yes
5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes	Yes
6. Are the main findings of the study clearly described?	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
8. Have all important AEs that may be a consequence of the intervention been reported?	Yes	Yes
9. Have the characteristics of patients lost to follow-up been described?	No	No
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No	NA
External Validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear	PY
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Unclear
13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Unclear	Unclear
Internal Validity		
14. Was an attempt made to blind study subjects to the intervention they have received?	No	NA
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	Unclear
16. If any of the results of the study were based on 'data dredging', was this made clear?	NA	NA
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Yes
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	NA
19. Was compliance with the intervention(s) reliable?	Yes	Yes
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Internal Validity – Confounding		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA

Question	Response	
	CL response	ERG
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	NA
23. Were study subjects randomised to intervention groups?	No	NA
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unclear	No
26. Were losses of patients to follow-up taken into account?	Unclear	No
Source: Table 22 of CL Response[3]. AEs = adverse events; ERG = Evidence Review Group; NA = not applicable		

ERG comment:

- Although the ERG considers that appropriate criteria were used to assess the methodological quality of the ARROW study, it normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.
- The Downs & Black checklist normally consists of five sections, however the final section and 27th question on 'Power' appears to have been left out in this assessment. Where the ERG's response differed from the company's response in questions 14 and 23, it was due to there being only one intervention group. The different responses for questions 10, 18, and 25 was because the study presents an interim analysis and hypothesis testing and adjustment for confounding would be expected in the final analysis. The dissimilar response in question 11 acknowledges that despite the change in protocol for patient eligibility to allow enrolment of treatment-naïve patients regardless of eligibility for standard therapies, it is unlikely that the study population would be unrepresentative of the wider disease population. The ERG's responses for question 15 is due to no information being given, and for question 26 is because the study methodology has not accounted for how missing data would be dealt with.
- In general, with the quality being marked as no or unclear in all four sections- reporting, external validity, internal validity, and confounding, the ARROW study does not appear to be a well-conducted (or reported) study.

3.2.5 Efficacy results from ARROW trial

3.2.5.1 Primary efficacy results

The primary efficacy endpoint in the ARROW trial is ORR, and analyses were based on the NSCLC MDP. Objective response rate in patients with RET fusion–positive NSCLC treated at 400 mg QD in the overall MDP (n=216) was 68.5% (95% confidence interval (CI): 61.9, 74.7) (Section B.2.6.1 of the CS). As presented in Table 3.8, ORR results were similar among patients in this population irrespective of prior treatment (treatment-naïve subgroup (n=68) ORR was 79.4% (95% CI: 67.9, 88.3); prior systemic treatment subgroup (n=148) ORR was 63.5% (95% CI: 55.2, 71.3)).

Table 3.10 ORR in patients with RET fusion–positive NSCLC

	Measurable Disease Population						
	All *RET* positive NSCLC n=216	Treatment-naïve			Prior Systemic Treatment		
		All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
ORR, % (95% CI)	69 (62, 75)	79 (68, 88)	74 (59, 87)	88 (69, 98)	64 (55, 71)	62 (53, 70)	73 (50, 89)
Best Overall Response, n (%)							
CR	9 (4)	4 (6)	4 (9)	0	5 (3)	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	89 (60)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	41 (28)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	7 (5)	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (4)	6 (5)	0

Source: Table 13 of the CS[28]
[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.
CI = confidence interval; CS = company submission; CR = complete response; NE = not estimated; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD = progressive disease; PR = partial response; RET = rearranged during transfection; SD = stable disease; % = percentage
Clinical cut-off date: 06 November 2020

ERG comment: Follow-up time for ORR has not been reported.

3.2.5.2 Secondary efficacy results

Duration of response: Analyses for duration of response (DOR) was based on the NSCLC MDP. Among all 148 patients in the MDP with a confirmed tumour response, median DOR was 22.3 months (95% CI: 15.1, NR) with 67.6% of the responding patients censored. As per Section B.2.6.2 of the CS, the Kaplan-Meier (KM) estimates for ongoing response were 84.0% (95% CI: 77.7, 90.3) at 6 months, 72.8% (95% CI: 64.8, 80.9) at 9 months, 63.2% (95% CI: 53.9, 72.6) at 12 months, and 53.7% (95% CI: 43.0, 64.3) at 18 months. For patients with a confirmed tumour response in the treatment-naïve subgroup (n=54), the median DOR was NR (95% CI: 9.0, NR) with 74.1% of the responding patients censored. Kaplan-Meier estimates for ongoing response were 83.8% (95% CI: 72.8, 94.8) at 6 months, 69.9% (95% CI: 54.3, 85.5) at 9 months, and 53.9% (95% CI: 33.9, 74.0) at 12 months. For the 94 patients with a confirmed tumour response in the prior systemic treatment subgroup, the median DOR was 22.3 months (95% CI: 15.1, NR) with 63.8% of the responding patients censored. Kaplan-Meier estimates for ongoing response were 84.0% (95% CI: 76.3, 91.7) at 6 months, 73.9% (95% CI: 64.4, 83.3) at 9 months, 66.2% (95% CI: 55.6, 76.8) at 12 months, and 55.3% (95% CI: 43.3, 67.3) at 18 months (See Table 3.9).

Clinical benefit rate: In the overall MDP (n=216), clinical benefit rate (CBR), representing the proportion of patients with stable disease duration ≥16 weeks or a confirmed response, was 76.9% (95% CI: 70.6, 82.3). In the treatment-naïve subgroup (n=68), CBR was 82.4% (95% CI: 71.2, 90.5) while CBR was 74.3% (95% CI: 66.5, 81.1) in the prior systemic treatment subgroup (n=148) (See Table 3.9).

Disease control rate: The proportion of patients with best overall response of SD or a confirmed response, known as the disease control rate (DCR) was 91.7% (95% CI: 87.1, 95.0 in the overall MDP

(n=216). In the treatment-naïve subgroup (n=68), DCR was 92.6% (95% CI: 83.7, 97.6) while DCR was 91.2% (95% CI: 85.4, 95.2) in the prior systemic treatment group (n=148) (See Table 3.9).

Table 3.11: Secondary efficacy endpoints in patients with RET fusion-positive NSCLC

	Measurable Disease Population						
		Treatment-naïve			Prior Systemic Treatment		
	All *RET* positive NSCLC n=216	All n=68	Pre-eligibility revision[a] n=43	Post-eligibility revision[a] n=25	All n=148	Prior platinum n=126	Prior non-platinum n=22
Duration of response							
DOR, months (95% CI)	22.3 (15.1, NR)	NR (9.0, NR)	11.0 (7.4, NR)	NR (NR, NR)	22.3 (15.1, NR)	22.3 (15.1, NR)	NR (9.2, NR)
Clinical benefit rate							
CBR, % (95% CI)	77 (71, 82)	82 (71, 91)	79 (64, 90)	88 (69, 98)	74 (67, 81)	74 (65, 81)	77 (55, 92)
Disease control rate							
DCR, % (95% CI)	92 (87, 95)	93 (84, 98)	91 (78, 97)	96 (80, 100)	91 (85, 95)	91 (85, 96)	91 (71, 99)

Sources: Tables 14, 15, and 16 of the CS[28]

[a] Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted.

CS = company submission; CBR = clinical benefit rate; CI = confidence interval; DCR = disease control rate; DOR = duration of response; NSCLC = non-small cell lung cancer; NR = not reported; RET = rearranged during transfection

Clinical cut-off date: 06 November 2020

Progression-free survival (PFS): Analyses for PFS were based on the unrestricted efficacy population. Overall, [redacted] patients in the unrestricted efficacy population had a median PFS of [redacted] months (95% CI: [redacted]). A total of 175 patients [redacted]) in this population were censored for analysis and [redacted] patients ([redacted]) had a PFS event. [redacted] reported to be [redacted] (Treatment-naïve subgroup (n=116): estimated median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored; prior systemic treatment subgroup (n=165): median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored) (See Table 3.12).

Table 3.12: PFS of patients with RET fusion–positive NSCLC in the unrestricted efficacy population

	Unrestricted Efficacy Population		
	All *RET* positive NSCLC n=281	Prior Systemic Treatment n=165	Treatment Naïve n=116
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Patients Censored, n (%)	[redacted]	[redacted]	[redacted]

	Unrestricted Efficacy Population		
	All *RET* positive NSCLC n=281	**Prior Systemic Treatment n=165**	**Treatment Naïve n=116**
PFS KM estimates, Months			
Median (95% CI[a])	[redacted]	[redacted]	[redacted]
PFS Rate, %			
3 months 95% CI	[redacted]	[redacted]	[redacted]
6 months 95% CI	[redacted]	[redacted]	[redacted]
9 months 95% CI	[redacted]	[redacted]	[redacted]
12 months 95% CI	[redacted]	[redacted]	[redacted]
18 months 95% CI	[redacted]	[redacted]	[redacted]
24 months 95% CI	[redacted]	[redacted]	[redacted]

Source: Table 17 of the CS[28]
CS = company submission; CI = confidence interval; KM = Kaplan–Meier; PFS = progression free survival; n = number; NSCLC = non-small cell lung cancer; PFS = progression free survival; RET = rearranged during transfection; % = percentage
[a]The 95% CI is based on Greenwood formula.
Clinical cut-off date is 6 November 2020.

Overall survival (OS): Analyses for OS were based on the unrestricted efficacy population. Among all [redacted] patients in the unrestricted efficacy population, [redacted]. Median follow-up was [redacted] months and [redacted] of patients were censored. Overall survival was reported to be similar regardless of prior treatment history (treatment-naïve subgroup [redacted]): KM estimated OS rate was [redacted] at both 6 months and 9 months, [redacted] at 12 months and [redacted] at 18 months; prior systemic treatment subgroup ([redacted]): KM estimated OS rate was [redacted] at 6 months, [redacted] at 9 months, [redacted] at 12 months and [redacted] at 18 months (See Table 3.13).

Table 3.13: Overall survival of patients with RET fusion–positive NSCLC in the unrestricted efficacy population

Parameter	Unrestricted Efficacy Population

	All *RET* positive NSCLC n=281	Prior Systemic Treatment n=165	Treatment Naïve n=116
Deaths, n (%)[a]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
Overall follow-up time KM estimates[a], months			
Median (95% CI[b])	[redacted]	[redacted]	[redacted]
OS KM estimate, Months			
Median (95% CI)	[redacted]	[redacted]	[redacted]
OS Rate, n (%)			
3 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

Source: Table 18 of the CS[28]
CS = company submission; CI = confidence interval; KM = Kaplan–Meier; n = number of patients; NSCLC = non-small cell lung cancer; OS = overall survival; RET = rearranged during transfection; % = percentage
[a]Overall follow-up time is based on reverse KM method. [b]The 95% CI is based on Greenwood formula.
Clinical cut-off date is 6 November 2020.

ERG comment:

- The results show that, limited by the low quality of the evidence, pralsetinib may improve oncological outcomes in patients with RET fusion–positive NSCLC.
- Follow-up times for CBR and DCR were not provided.
- The CS stated that *"the efficacy population was the primary population for efficacy analysis"* (Table 9 of the CS), and Tables 10 and 11 in the CS detailed plans for analysis to be performed in the efficacy population, however no results have been published in this population.[1] The company offered no justification for this deviation, or preference of results in the MDP.
- The ERG notes that at the cut-off point of 6 November 2020, the data on long-term survival is immature.

3.3 Safety results from ARROW trial

This section considers the information about AEs provided in the CS. Safety results for the overall safety population with all tumour types treated at 400 mg QD of pralsetinib (n=528), and the safety population of patients with NSCLC treated at 400 mg QD (n=281) at a data cut-off (6 November 2020), and AE data stratified by pre-treatment status of patients, is summarised in Table 3.14. Similar proportions of patients experienced serious AEs (SAEs) (54.5% in the overall safety population and

59.1% in the RET fusion-positive NSCLC population), ≥Grade 3 treatment-related AEs (56.1% vs. 55.2%) and deaths due to AEs (13.5% in both populations). According to the CS, pralsetinib was found to generally be well tolerated in the overall safety population and in patients with RET fusion–positive NSCLC treated with 400 mg QD.[28]

Table 3.14: Summary of AEs

Parameter, n (%)	Overall (All tumour types) n=528	*RET* fusion-positive NSCLC n=281	Prior systemic treatment [redacted]	No prior systemic treatment [redacted]
Any AE	525 (99.4)	279 (99.3)	[redacted]	[redacted]
≥Grade 3	406 (76.9)	212 (75.4)	[redacted]	[redacted]
TRAEs	493 (93.4)	264 (94.0)	[redacted]	[redacted]
≥Grade 3	296 (56.1)	155 (55.2)	[redacted]	[redacted]
SAE	288 (54.5)	166 (59.1)	[redacted]	[redacted]
≥Grade 3	251 (47.5)	137 (48.8)	[redacted]	[redacted]
Related SAEs	111 (21.0)	70 (24.9)	[redacted]	[redacted]
Deaths due to AEs	71 (13.4)	38 (13.5)	[redacted]	[redacted]
Deaths related to pralsetinib	6 (1.1)	2 (<1)	[redacted]	[redacted]

Sources: Table 34 of CL Response[3]
AE = adverse event; CL = clarification letter; n = number of patients; NSCLC = non-small cell lung cancer; RET = rearranged during transfection; SAE = serious adverse event; TRAE = treatment-related adverse event; % = percentage

There were several differences between results reported in the CS [28]and clarification letter response [3] however the company did state in the CS that, "*the current safety data presented are subject to regulatory changes and further safety analyses may come available during the EMA filing process*".[16] Hence, the ERG reported the safety results published in the clarification letter response where appropriate.[3]

A summary of treatment-related AEs (TRAEs) with ≥10% incidence is presented in Table 3.15. 493 patients (93.4%) in the overall safety population and 264 (94.0%) in patients with RET fusion–positive NSCLC treated at 400 mg QD experienced ≥1 TRAEs and 108 (20.5%) in the overall safety population and 166 (59.1%) in patients with RET fusion–positive NSCLC treated at 400 mg QD experienced treatment related SAEs.[28] In the safety population and for patients with RET fusion–positive NSCLC treated at 400 mg QD, the most common TRAEs were aspartate aminotransferase (AST) increased (39.0% vs. 40.6%), anaemia (33.9% vs. 35.9%), alanine aminotransferase (ALT) increased (28.8% vs. 29.6%), neutrophil count decreased (22.7% vs. 28.1%), constipation (26.9% vs. 26%), hypertension (25.2% vs. 24.9%) and white blood cell (WBC) count decreased (25.2% vs. 24.9%).[28] All other TRAEs for the overall safety population occurred in <25% of patients while for patients with RET fusion–positive NSCLC treated at 400 mg QD, all other TRAEs occurred in <20% of patients.[28] A summary of AEs of Grade ≥3 with ≥10% incidence is presented in Table 3.15. AEs of Grade ≥3 were reported by 406 patients (76.9%) in the overall safety population and by 212 patients (75.4%) with RET fusion–positive NSCLC treated at 400 mg QD. The most common AEs of Grade ≥3 (reported in ≥10% patients) in the overall safety population and for patients with RET fusion–positive NSCLC treated at 400 mg QD were anaemia (17.2% vs. 16.4%), hypertension (16.1% vs. 16%), neutropenia (11.2% vs. 10.7%) and neutrophil count decreased (9.7% vs. 12.8%).[28] Sixty-six patients

(12.5%) died during the study due to AEs, including 35 patients with RET fusion–positive NSCLC (12.5%).[28]

In the clarification letter, the ERG asked the company to "*provide an indirect treatment comparison for adverse events for the safety population of participants with RET fusion-positive NSCLC*" [18] In their response, the company stated that "*indirect treatment comparisons of safety outcomes are challenging*" due to a number of factors due to different follow-up time between trials and limited data.

Table 3.15: Summary of AEs (overall safety population and patients with NSCLC treated at 400 mg QD)

Preferred term, n (%)	Overall (all tumour types) n=528	*RET* fusion–positive NSCLC n=281
Grade ≥3 AE with ≥10% incidence, n (%)		
Any Grade ≥3 AE	406 (76.9)	212 (75.4)
Anaemia	91 (17.2)	46 (16.4)
Hypertension	85 (16.1)	45 (16.0)
Neutropenia	59 (11.2)	30 (10.7)
Neutrophil count decreased	51 (9.7)	36 (12.8)
Treatment-related adverse event, TRAEs with ≥10% incidence, n (%)		
Patients with Any TRAE	493 (93.4)	264 (94.0)
AST increased	206 (39.0)	114 (40.6)
Anaemia	179 (33.9)	101 (35.9)
ALT increased	152 (28.8)	84 (29.6)
Neutrophil count decreased	120 (22.7)	79 (28.1)
Constipation	142 (26.9)	73 (26.0)
Hypertension	133 (25.2)	70 (24.9)
WBC count decreased	133 (25.2)	70 (24.9)
Neutropenia	109 (20.6)	58 (20.6)
SAEs occurring in ≥2% patients, n (%)		
Patients with SAEs	288 (54.5)	166 (59.1)
Pneumonia	52 (9.8)	33 (11.7)
Disease progression	41 (7.8)	21 (7.5)
Pneumonitis	24 (4.5)	13 (4.6)
Anaemia	20 (3.8)	9 (3.2)
Sepsis	15 (2.8)	8 (2.8)
Pyrexia	12 (2.3)	8 (2.8)
Dyspnoea	10 (1.9)	6 (2.1)
Urinary tract infection	18 (3.4)	6 (2.1)
Pleural effusion	10 (1.9)	6 (2.1)

Sources: Tables 28 and 29 of the CS[28]
Note: AEs were coded using MedDRA 19.1. If a patient had multiple occurrences of an AE, the patient was presented only once in the respective patient count. The events are presented in a decreasing frequency as per the overall safety population.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; n = number of people treated; NSCLC = non-small cell lung cancer; QD = once daily; SAE = serious adverse event; TRAE = treatment-related adverse event; WBC = white blood cell; % = percentage

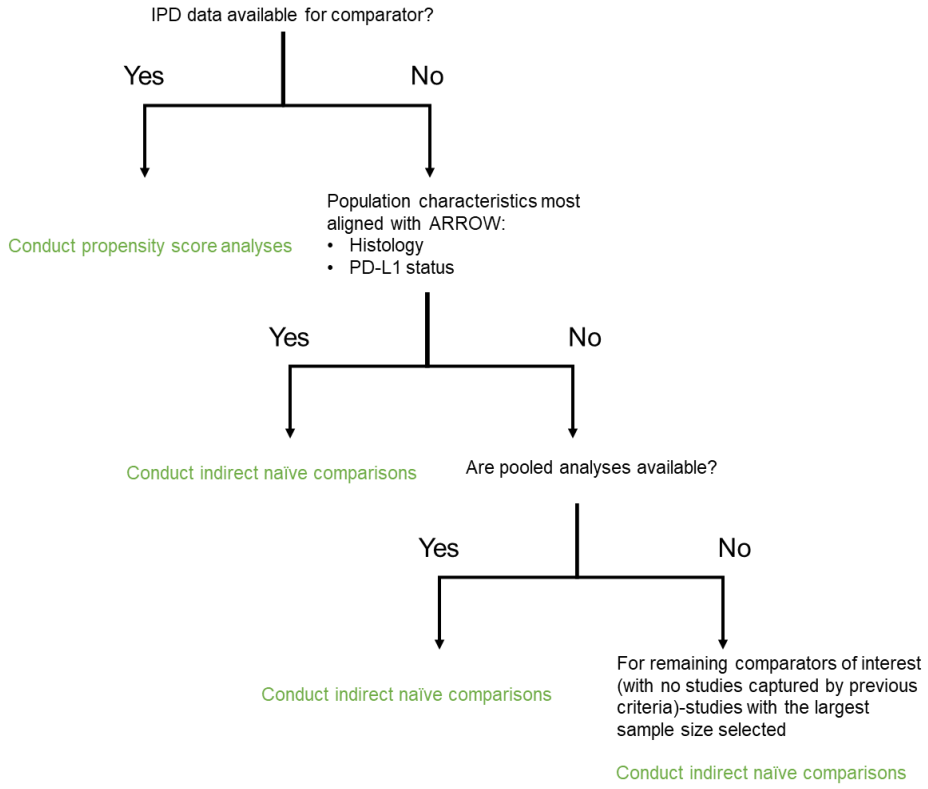
ERG comment:

- The ERG notes that there are no comparative safety data for pralsetinib versus comparators listed in the NICE final scope for the treatment of patients with advanced, unresectable, RET-altered NSCLC, due to available evidence being a single arm study.
- The ERG concurs those comparisons across trials in general can be challenging, however, the challenges do not preclude rigorous indirect treatment comparison for adverse events.

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

[redacted] Therefore, the company chose to make comparison in the WT population, citing Hess et al 2021 to support little difference in prognosis once prognostic factors have been controlled for.[29] The company employed a stepwise process to obtain data sources for comparison with the various comparators in each of the population subgroups, as shown in Figure 3.1.

Figure 3.1: Overview of methodology for the selection of studies for the comparative analyses



An individual patient data (IPD) analysis using real-world data was prioritised, and the company chose the Flatiron study for the comparison with Pembrolizumab + pemetrexed + chemotherapy and Pembrolizumab monotherapy.[30] In addition, an SLR was conducted to inform the other comparisons in the WT population employing the stepwise process. A summary of the sources used for each comparison after following this stepwise process plus the results of analyses conducted is shown in Table 3.16.

Table 3.16: Summary of hazard ratios vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR (95% CIs)	PFS HR (95% CIs)	TTD HR (95% CIs)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)[30]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)[30]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	OAK trial (propensity score weighting ATT)[31, 32]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	LUME-Lung 1 (naïve comparison); PFS assumed equal to docetaxel monotherapy[33]
Pemetrexed + carboplatin	[redacted]	[redacted]	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison)[24]

Source: Table 24, CS[3]

CS = company submission; EMD = enhanced data mart; HR = hazard ratio; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation

Table 3.17 provides the details of the studies obtained using the SLR, OAK,[31, 32] GOIRC trial[24] and LUME-Lung[33] as relevant studies to inform the indirect treatment comparison (ITC) of pralsetinib versus docetaxel monotherapy, pemetrexed plus carboplatin and docetaxel plus nintedanib respectively. Table 3.18 gives an overview of the baseline characteristics of these studies.

Table 3.17: Overview of study designs of OAK, GOIRC and LUME-Lung 1

Study characteristics	ARROW (NCT03037385)[27]	Docetaxel monotherapy OAK trial[32]	Pemetrexed + carboplatin (GOIRC)[24]	Docetaxel + nintedanib (LUME-Lung 1)[33]
Blinding	Open label	Open label	Open label	Double-blinded
Inclusion criteria	• ≥18 years of age • Locally advanced or metastatic NSCLC with a RET fusion previously treated (or untreated) with a platinum-based chemotherapy • Non-resectable disease • Measurable disease per RECIST v1.1 • ECOG zero to one	• Squamous or non-squamous NSCLC • ≥18 years • Measurable disease per RECIST criteria • ECOG zero or one • One to two previous cytotoxic chemotherapy regimens for stage IIIB or IV NSCLC	• ≥18 years • Non-squamous only • ECOG PS ≤ 2 • Histologically or cytologically confirmed NSCLC • Stage IIIB or IV NSCLC • At least one measurable target lesion per RECIST criteria • Disease progression after one line of	• Male or female patients (>18 years) • Histologically confirmed locally advanced or metastatic NSCLC • ECOG zero to one • One prior line of systemic anticancer therapy

Study characteristics	ARROW (NCT03037385)[27]	Docetaxel monotherapy OAK trial[32]	Pemetrexed + carboplatin (GOIRC)[24]	Docetaxel + nintedanib (LUME-Lung 1)[33]
			systemic anticancer therapy	
Key exclusion criteria	• Primary driver alteration other than RET • Platelet count < 75 × 10^9/L • Absolute neutrophil count < 1.0 × 10^9/L • Haemoglobin < 9.0 g/dL • Aspartate aminotransferase or alanine aminotransferase > 3 × the upper limit of normal if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present • Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease • Measured creatinine clearance < 40 mL/min • Total serum phosphorous > 5.5 mg/dL • History of prolonged QT syndrome • Uncontrolled, cardiovascular disease • CNS metastases • Interstitial lung disease or interstitial pneumonitis • Any systemic anticancer or immunotherapy therapy • Previous *RET* inhibitor treatment	• History of autoimmune disease • Previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway	• Prior treatment with pemetrexed • Pregnant or lactating • Any underlying medical condition that might be aggravated by treatment or which cannot be controlled • Symptomatic brain metastases • History of another malignancy within the past 5 years except basal cell carcinoma of the skin or carcinoma in situ of the cervix • Concomitant treatment with any other anticancer drug	• Active brain metastases • Received >1 prior anti-cancer drug regimen for advanced or metastatic NSCLC • Prior treatment with a VEGFR inhibitor (other than bevacizumab) or docetaxel

Study characteristics	ARROW (NCT03037385)[27]	Docetaxel monotherapy OAK trial[32]	Pemetrexed + carboplatin (GOIRC)[24]	Docetaxel + nintedanib (LUME-Lung 1)[33]
	• Received neutrophil growth factor support or major surgical procedure within 14 days of the first dose of study drug • History of another primary malignancy that has been diagnosed or required therapy			
Primary endpoint	• ORR • ORR by RECIST v1.1 • Safety and tolerability	• OS • PD-L1-expression	• PFS • RR	• PFS
Key secondary endpoints	• DOR • CBR • DCR • PFS • OS	-	• Toxicity	• OS
CD137 = cluster of differentiation 137; CBR = clinical benefit rate; CTLA4 = cytotoxic-T-lymphocyte-associated antigen 4; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance score; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD-L1 = programmed death-ligand 1; RR = response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; RET = rearranged during transfection; VEGFR = vascular endothelial growth factor receptor				

Table 3.18: Comparison of baseline characteristics in ARROW, OAK, GOIRC and LUME-Lung 1 trials

Baseline characteristics[a]	ARROW (NCT03037385) (N=233)[27]	Docetaxel monotherapy OAK trial (N=425) [32]	Pemetrexed + carboplatin (GOIRC) (N=119)[24]	Docetaxel + nintedanib (LUME-Lung 1) (N=322)[33c]
Age	60 (median)	64 (median)	64 (median)	58.5 (median)
Gender (% female)	52.4%	39%	72.3%	37%
Brain metastases (%)	37.3%	NR	NR	8%
Performance status (ECOG or WHO; % PS 1)	63.9%	62%	37.8%	70%
Race (% white)	51.9%	70%	NR	NR[a]
Anti-PD-(L)1 in prior line(s)	29.6%	NR	NR	0%

Baseline characteristics[a]	ARROW (NCT03037385) (N=233)[27]	Docetaxel monotherapy OAK trial (N=425) [32]	Pemetrexed + carboplatin (GOIRC) (N=119)[24]	Docetaxel + nintedanib (LUME-Lung 1) (N=322)[33c]
Number of prior lines (% with 1/2/3 prior lines)	59.2% had chemotherapy	1 line 75% 2 lines 25%	NR	Mostly 1 prior line[b]
Metastatic disease at baseline	NR	NR	NR	90%
Histology (% non-squamous)	96.1% had adenocarcinoma	74%	71.4% had adenocarcinoma	100%[c]
Smoking status (% ever smoker)	33.5%	67%	NR	64%
PD-L1 expression at baseline (<5% (vs. >5%))	NR	NR	NR	NR

Based on Table 8 of the CS [1]
[a]Race was not reported, the trial was non-US based and run mainly in Europe (71% of patients) as well as Asia;
[b]LUME-Lung 1 included patients with a prior platinum-based therapy and allowed adjuvant/neoadjuvant as line of therapy;
[c]Based on the subpopulation of interest (adenocarcinoma)
CS = company submission; ECOG = European Co-operative Oncology Group; NR = not reported; PD-L1 = programmed death-ligand 1; PS = performance status; WHO = World Health Organization; % = percentage

ERG comment:

- The ERG notes the differences between the studies; and it is not possible to match for all of these differences which might have an impact on the validity of the findings of any ITC. For example, the OAK trial included squamous or non-squamous NSCLC whereas the GOIRC trial included non-squamous NSCLC only.[24, 32] The LUME-Lung trial was double blinded and the remaining three trials were open-label. The LUME-Lung trial, ARROW and OAK trial included patients with a ECOG PS of zero or one whereas patients in the GOIRC trial had a ECOG PS ≤ 2.
- The ERG also notes the baseline differences between the studies. There were more females in the GOIRC study as compared with the LUME-Lung 1 trial i.e., 72.3% vs. 37%. Only 8% of patients had brain metastases in the LUME-Lung 1 trial vs. 37.3% in the ARROW study.[27] Also ECOG PS of one was the lowest in the GOIRC trial compared with the other three studies. Metastatic disease at baseline was not reported in three trials. [24, 27, 32]
- Overall, the ERG considers that the assumption of equivalent prognosis between RET+ and – seems plausible, after controlling for other prognostic factors.[29] This means that the WT SLR could be valuable as a source of studies for comparison with pralsetinib.
- Despite the limitations noted above, the company approach of, where possible, conducting and an individual patient data (IPD) analysis, also seems reasonable, given, all things being equal, its superiority to either a naïve comparison or a MAIC.[34] This is because of the ability to adjust for many prognostic characteristics and the relatively large sample size of at least the Flatiron study (n=5,000+ or at least 350 depending on comparator).[1] The comparison with docetaxel monotherapy was also with IPD, although from the OAK trial.[32] This means that comparisons with docetaxel plus nintedanib and pemetrexed plus carboplatin are the only ones where IPD did not appear to be available.[1] However, the ERG would argue that Flatiron could have been used for platinum-based chemotherapy +/- pemetrexed given that this regimen was used in more patients than both

pembrolizumab plus pemetrexed plus chemotherapy and pembrolizumab monotherapy (16.1% vs. 14.1% and 7.6%).[29] Therefore, eliminating the ones where IPD could be available, the only comparison that might be affected by selectivity in the step-wise approach adopted for the WT SLR would be docetaxel plus nintedanib, but the company found only one study. [redacted] As stated in Section 3.1, the ERG questioned the exclusion of the Chinese study on the basis of sample size and ethnicity.[22] Nevertheless, one could reasonably conclude that the stepwise approach would have little if any material effect on clinical effectiveness once Flatiron use has been exhausted. In conclusion, what remains as a key issue in terms of data source for estimating clinical effectiveness is that for comparison with platinum-based chemotherapy +/- pemetrexed and the ERG would recommend an analysis be conducted using Flatiron.

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

[redacted]

Individual patient data analysis was attempted using Flatiron in the RET mutation positive population. However, after application of study eligibility criteria, 10 untreated and six pre-treated participants were identified: pembrolizumab plus chemotherapy ([redacted]), platinum-based chemotherapy ([redacted]), immunotherapy monotherapy ([redacted]) and other ([redacted]). In the untreated analysis, results favoured pralsetinib over best available therapy ([redacted]).The company stated that due to the test being underpowered, results were not statistically significant, and CIs crossed one. They concluded that, given the sample size limitations, this patient population was not considered suitable to inform decision making.

Therefore, in the WT populations, as summarised in Table 3.15, the company conducted three types of comparative analysis:

1) Propensity score weighting (PSW) using Flatiron for:
    a. Pembrolizumab plus pemetrexed plus chemotherapy
    b. Pembrolizumab monotherapy

2) PSW using OAK trial for: Docetaxel monotherapy

3) Naïve comparisons for:
    a. Docetaxel plus nintedanib
    b. Pemetrexed plus carboplatin

The following explanation of methods and results has been summarised from the CS. Full details of the company's methods can be found in Section B.2.9.5 of the CS.[1]

3.4.1. Propensity score weighting (PSW) using Flatiron

3.4.1.1 Methods

This indirect treatment comparison involved two comparisons within the untreated population: pralsetinib versus pembrolizumab plus pemetrexed plus chemotherapy; and pralsetinib versus pembrolizumab monotherapy (Section B.2.9.5 of the CS).[1] The data for patients receiving pralsetinib was derived from the ARROW study, using the unrestricted efficacy population from the 6 November 2020 data cut. The Flatiron Health patients were eligible for this analysis if they were from the Enhanced Data Mart (EDM) database, diagnosed with locally advanced or metastatic NSCLC between 1 January 2011 and 31 March 2020 and initiated first or second line therapy at a Flatiron Health clinic between 2017 and 2019 (to be contemporary to ARROW). Patients were required to have at least 6 months of potential follow-up (i.e., treatment initiation date no later than 1 September 2019). It is possible that some patients in the EDM were *RET*-positive, but it was assumed that most EDM patients were RET-negative. The participant selection criteria for the analysis are summarised in Table 3.19.

Table 3.19: Participant selection criteria for PSW using Flatiron

Inclusion criteria	Exclusion criteria
***RET*-positive patients from ARROW**	
• Unresectable locally advanced or metastatic NSCLC with *RET fusion-positive* tissue sample • Non-squamous histology (although for each comparison, ARROW has 'handful' of patients with squamous histology) • ECOG or 0 or 1 with no more than one participant with value > 1*	None stated
WT patients from Flatiron EDM database	
• Unresectable locally advanced or metastatic NSCLC • Non-squamous histology • ECOG or zero or one • Line start date falling between 2017 and 2019 (to be congruent with ARROW time frame)	• >90-day gap between advanced diagnosis and first visit or medication administration • Prior use of pralsetinib or selpercatinib or clinical study drugs in any line • Known driver mutation (EGFR, ALK, ROS1 or BRAF) at index date • Index date less than 6 months before EDM cut-off date • Missing entry or 'Not reported' entered for stage at initial diagnosis or smoking status

Based on information in Section B.2.9.5 in the CS[1]
**"….if EDM patients with ECOG > 1 are included, the non-overlap between the two datasets becomes an issue that cannot be solved by statistical weighting methods since we can only adjust for ECOG values common in both arms"* from Section B.2.9.5 in the CS[1]
ALK = anaplastic lymphoma kinase; BRAF = B-raf (mutation); CS = company submission; ECOG = Eastern Cooperative Oncology Group; EDM = Enhanced Data Mart; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PSW = propensity score weighting; RET = rearranged during transfection; ROS1 = c-ros oncogene 1)

The data for the ARROW pralsetinib arm and EDM comparator arm were pooled. A logistic regression propensity score model was estimated by regressing a pralsetinib treatment indicator on baseline covariates. Propensity scores were calculated for each patient using the fitted values from the propensity score model. Inverse probability of treatment weighting (IPTW) weights for the average treatment effect in treated participants (ATT) estimates were computed by assigning each patient in the pralsetinib arm a weight of one and each patient in the comparator arm a weight of [propensity

score]/(1 – [propensity score]). The effective sample size was calculated by taking the square of the sum of all weights divided by the summation of each of the weights squared.[35] Participants with a weight exceeding three were trimmed. The use of a fixed threshold was motivated by the observation that there were no scenarios where a large number of patients had large weights.[1] The ERG asked the company to provide the reasoning for the threshold of three for the trimming of propensity scores. The company replied that *"All propensity score descriptive statistics below are based on weights trimmed at a threshold of three. The threshold was based on visual inspection of the distribution of weights."*[3]

All results presented for the IPTW analysis were produced after trimming participants with large weights.[3637] Next, IPTW-weighted Cox proportional hazards regression models were used to estimate hazard ratios between the pralsetinib and comparator arms and 95% CIs were computed using robust standard errors. Sensitivity analysis using matching instead of IPTW was also conducted and is presented in the SLR report.[1]

3.4.1.2 Results

The Flatiron database provided sufficient patient populations to conduct untreated comparisons against pembrolizumab plus pemetrexed plus carboplatin (where carboplatin was assumed to represent chemotherapy in UK clinical practice) and pembrolizumab monotherapy.[1]

3.4.1.2.1 Untreated pembrolizumab plus pemetrexed plus chemotherapy

Table 3.20 (below) shows the baseline characteristics for pralsetinib and pembrolizumab plus pemetrexed plus chemotherapy before and after the IPTW (ATT) adjustment. Following IPTW, balance was achieved among the matching covariates. The metastases-related variables are highly imbalanced, though these are suspected to be unreliable due to under recording in the Flatiron EDM database.[1]

Table 3.20: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given pembrolizumab + pemetrexed + chemotherapy in untreated setting without and with adjustment

Pralsetinib demonstrates a statistically significant improvement in OS (HR [redacted], 95% CI [redacted], [redacted]) compared to the primary comparator pembrolizumab plus pemetrexed plus chemotherapy. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]). Figures 3.2 to 3.4 show the KM curves for pralsetinib compared to pembrolizumab plus pemetrexed plus chemotherapy and the impact of the IPTW.

Figure 3.2: Kaplan-Meier estimates using IPTW for OS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 25 of the CS[1]
CS = company submission, EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; OS = overall survival

Table 3.21: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given pembrolizumab + pemetrexed + chemotherapy in untreated setting without and with adjustment

	Level	Without adjustment			With adjustment			Adjusted
		Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	
n		[redacted]	[redacted]		[redacted]*			
Age (%)	< 65	[redacted]	[redacted]	0.4	[redacted]	[redacted]	0.015	Y
	≥ 65	[redacted]	[redacted]		[redacted]	[redacted]		
Sex (%)	F	[redacted]	[redacted]	0.187	[redacted]	[redacted]	0.007	Y
	M	[redacted]	[redacted]		[redacted]	[redacted]		

	Level	Without adjustment			With adjustment			Adjusted
		Pembrolizumab + pemetrexed + hemotherapy	Pralsetinib	SMD	Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	1.25	[redacted]	[redacted]	0.017	Y
	No history of smoking	[redacted]	[redacted]		[redacted]	[redacted]		
ECOG (%)	0	[redacted]	[redacted]	0.191	[redacted]	[redacted]	0.037	Y
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.148	[redacted]	[redacted]	0.042	Y
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.013	[redacted]	[redacted]	0.028	Y
	STAGE IV	[redacted]	[redacted]		[redacted]	[redacted]		
Race (%)	White	[redacted]	[redacted]	0.573	[redacted]	[redacted]	0.061	Y
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
	Unknown	[redacted]	[redacted]		[redacted]	[redacted]		
Sum of total metastases		[redacted]	[redacted]	1.534	[redacted]	[redacted]	1.529	N

	Level	Without adjustment			With adjustment			Adjusted
		Pembrolizumab + pemetrexed + hemotherapy	Pralsetinib	SMD	Pembrolizumab + pemetrexed + chemotherapy	Pralsetinib	SMD	
(median [IQR])								
Metastases (%)	Isolated brain/ CNS site	[redacted]	[redacted]	1.61	[redacted]	[redacted]	1.672	N
	None	[redacted]	[redacted]		[redacted]	[redacted]		
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
Brain/ CNS metastasis only (%)	0	[redacted]	[redacted]	0.333	[redacted]	[redacted]	0.383	N
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Liver metastasis only (%)	0	[redacted]	[redacted]	0.25	[redacted]	[redacted]	0.32	N

Based on Table 21 of the CS.[1]

CS = company submission; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; F = female; IQR = interquartile range; IQR = interquartile range M = male; n = number of patients treated; SMD = standardised mean difference; % = percentage

*Effective sample size (ESS)

Figure 3.3: Kaplan-Meier estimates using IPTW for PFS comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 26 of the CS[1]
CS = company submission; EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; PFS = progression free survival

Figure 3.4: Kaplan-Meier estimates using IPTW for TTD comparing pralsetinib with pembrolizumab + pemetrexed + chemotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 27 of the CS[1]
CS = company submission; EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; TTD = time to treatment discontinuation

3.4.1.2.2 Untreated pembrolizumab monotherapy

Table 3.21 (below) shows the baseline characteristics for pralsetinib and pembrolizumab monotherapy before and after the IPTW (ATT) adjustment. Following IPTW, balance was achieved for the majority of matching covariates though age, smoking history and race remain imbalanced. The metastases-related variables are highly imbalanced, though these are suspected to be unreliable due to under recording in the Flatiron EDM database.

Pralsetinib demonstrates a statistically significant improvement in OS (HR [redacted], 95% CI [redacted], [redacted]) compared to pembrolizumab monotherapy. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted], [redacted]).

Figures 3.5 to 3.7 (inclusive) show the KM curves for pralsetinib compared to pembrolizumab monotherapy and the impact of the IPTW adjustment (ATT).[1]

Table 3.22: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given pembrolizumab monotherapy in untreated setting without and with adjustment

	Level	Without adjustment			With adjustment			
		Pembrolizumab monotherapy	Pralsetinib	SMD	Pembrolizumab monotherapy	Pralsetinib	SMD	Adjusted Pembrolizumab monotherapy
N		[redacted]	[redacted]		[redacted]*			
Age (%)	< 65	[redacted]	[redacted]	0.4	[redacted]	[redacted]	0.23	Y
	≥ 65	[redacted]	[redacted]		[redacted]	[redacted]		
Sex (%)	F	[redacted]	[redacted]	0.187	[redacted]	[redacted]	0.072	Y
	M	[redacted]	[redacted]		[redacted]	[redacted]		
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	1.25	[redacted]	[redacted]	0.192	Y
	No history of smoking	[redacted]	[redacted]		[redacted]	[redacted]		
ECOG (%)	0	[redacted]	[redacted]	0.191	[redacted]	[redacted]	0.075	Y
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.148	[redacted]	[redacted]	0.078	Y
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.013	[redacted]	[redacted]	0.038	Y
	STAGE IV	[redacted]	[redacted]		[redacted]	[redacted]		
Race (%)	White	[redacted]	[redacted]	0.573	[redacted]	[redacted]	0.199	Y
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
	Unknown	[redacted]	[redacted]		[redacted]	[redacted]		

	Level	Without adjustment			With adjustment			
		Pembrolizumab monotherapy	Pralsetinib	SMD	Pembrolizumab monotherapy	Pralsetinib	SMD	Adjusted Pembrolizumab monotherapy
Sum of total metastases (median [IQR])		[redacted]	[redacted]	1.534	[redacted]	[redacted]	1.728	N
Metastases (%)	Isolated brain/CNS site	[redacted]	[redacted]	1.61	[redacted]	[redacted]	1.872	N
	None	[redacted]	[redacted]		[redacted]	[redacted]		
	Other	[redacted]	[redacted]		[redacted]	[redacted]		
Brain/CNS metastasis only (%)	0	[redacted]	[redacted]	0.333	[redacted]	[redacted]	0.241	N
	1	[redacted]	[redacted]		[redacted]	[redacted]		
Liver metastasis only (%)	0	[redacted]	[redacted]	0.25	[redacted]	[redacted]	0.398	N

Based on Table 22 of the CS[1]

CS = company submission; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; F = female; IQR = interquartile range; IQR = interquartile range M = male; n = number of patients treated; SMD = standardised mean difference; % = percentage

*Effective sample size (ESS)

Figure 3.5: Kaplan-Meier estimates using IPTW for OS comparing pralsetinib with pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 28 of the CS[1]
CS = company submission; EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; OS = overall survival

Figure 3.6: Kaplan-Meier estimates using IPTW for PFS comparing pralsetinib with

pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 29 of the CS[1]
EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; PFS = progression free survival

Figure 3.7: Kaplan-Meier estimates using IPTW for TTD comparing pralsetinib with

pembrolizumab monotherapy in untreated setting (ARROW vs. Flatiron EDM database)

Based on Figure 30 of the CS[1]
EDM = Enhanced Data Mart; IPTW = inverse probability of treatment weighting; TTD = time to treatment discontinuation

3.4.1.2.3 Summary of results for PSW using Flatiron

Table 3.23 (below) provides a summary of hazard ratios for the two above comparisons.

Table 3.23: Summary of hazard ratios vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR	PFS HR	TTD HR	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (propensity score weighting ATT)
Source is Table 23 of the CS[1] Where hazard ratio <1 favours pralsetinib ATT = average treatment-effect on treated; CS = company submission; EDM = Enhanced Data Mart; HR = hazard ratio, PFS = progression-free survival; OS = overall survival; TTD = time to treatment discontinuation				

ERG comment: The ERG asked the company to elaborate on whether the choice of variables in the PSW (that underpinned the hazard ratio estimates) was sufficient and appropriate. The company confirmed that the adjusted baseline characteristics included age, sex, smoking status, ECOG, time from initial diagnosis to first dose, stage at diagnosis and race. The company consulted an advisory board of

clinical experts who confirmed the prognostic importance of the variables and agreed that the untreated participants from ARROW were clinically comparable with the Flatiron participants, after matching.[3]

The ERG asked the company to consider adding body mass index (BMI) or a similar variable to account for potential underlying general health risks between the populations (or justify the decision for not doing this). The company replied that, in light of sample size ([redacted] untreated and [redacted] pre-treated), the analysis was limited in terms of the number of covariates that could be included and also highlighted the risk of overfitting the model if too many covariates are used.[3]

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG assessed the quality of the ARROW trial independently using the Downs and Black checklist.[26]

3.6 Conclusions of the clinical effectiveness section

The main evidence for the clinical effectiveness of pralsetinib was from the ARROW trial (BLU-667-1101 study).[2] The ARROW trial is an ongoing, Phase I/II, multicentre, non-randomised, multi-cohort, first-in-human (FIH) open-label study of patients with advanced, unresectable, *RET* fusion-positive non-small cell lung cancer (NSCLC) and other *RET* altered solid tumours.[28]

The primary aim of the ARROW study was to determine the MTD, recommended phase 2 dose (RP2D), and the safety and tolerability of pralsetinib. Patient cohorts consisted of one to three patients for pralsetinib at 30 mg, 60 mg, and 100 mg QD and three to six patients for higher dose levels, 200 mg, 300 mg, 400 mg, and 600 mg, as well as for the BID schedule. Phase I continued until the recommended RP2D was determined, upon which the Phase 2 expansion stage began.[2, 28]

Six analysis sets were considered in the ARROW trial:

- Safety population: all patients who were initiated with 400 mg QD pralsetinib;
- Efficacy population: all patients with *RET* fusion–positive NSCLC in the safety population who were initiated with 400 mg pralsetinib on or prior to 22 May 2020;
- *RET*-altered MDP;
- Unrestricted efficacy population; and
- Response-evaluable population.

In the MDP population used for the primary efficacy analysis, most patients were female (51.9%), <65 years of age (66.5%), and white (52.3%) or Asian (38.4%), and had an ECOG PS of zero or one, with just six (2.8%) having an ECOG PS of two.[28] In the efficacy population, most patients were female (52.4%), <65 years of age (62.2%), white (51.9%) or Asian (39.5%), and had an ECOG PS of zero or one, with just six (2.6%) having an ECOG PS of two.[28]

As it was unclear whether two independent reviewers assessed the quality of the ARROW study, the ERG did their own using the Downs and Black checklist.[26] Due to the quality being marked down in all four sections - reporting, external validity, internal validity, and internal validity – confounding, the ERG's assessment is that the ARROW study does not appear to be a well-conducted, non-comparative observational study.

A median follow-up time was not reported for the ORR which was based on the NSCLC MDP population in patients with RET fusion–positive NSCLC treated at 400 mg QD in the overall MDP (n=216) was 68.5% (95% CI: 61.9, 74.7). The ORR results were similar among patients in this

population irrespective of prior treatment (treatment-naïve subgroup (n=68) ORR was 79.4% (95% CI: 67.9, 88.3); prior systemic treatment subgroup (n=148) ORR was 63.5% (95% CI: 55.2, 71.3)).

Among all 148 patients in the MDP with a confirmed tumour response, the median DOR was 22.3 months (95% CI: 15.1, NR) with 67.6% of the responding patients censored. For patients with a confirmed tumour response in the treatment-naïve subgroup (n=54), the median DOR was NR (95% CI: 9.0, NR) with 74.1% of the responding patients censored. For the 94 patients with a confirmed tumour response in the prior systemic treatment subgroup, the median DOR was 22.3 months (95% CI: 15.1, NR) with 63.8% of the responding patients censored. Kaplan-Meier estimates for ongoing response were 84.0% (95% CI: 76.3, 91.7) at 6 months, 73.9% (95% CI: 64.4, 83.3) at 9 months, 66.2% (95% CI: 55.6, 76.8) at 12 months, and 55.3% (95% CI: 43.3, 67.3) at 18 months (See Table 3.9).

In the overall MDP (n=216), the CBR, representing the proportion of patients with SD duration ≥16 weeks or a confirmed response, was 76.9% (95% CI: 70.6, 82.3). In the treatment-naïve subgroup (n=68), CBR was 82.4% (95% CI: 71.2, 90.5) while CBR was 74.3% (95% CI: 66.5, 81.1) in the prior systemic treatment subgroup (n=148). The proportion of patients with best overall response of SD or a confirmed response, known as the DCR was 91.7% (95% CI: 87.1, 95.0 in the overall MDP (n=216). In the treatment-naïve subgroup (n=68), DCR was 92.6% (95% CI: 83.7, 97.6) while DCR was 91.2% (95% CI: 85.4, 95.2) in the prior systemic treatment group (n=148). Median follow-up times for CBR and DCR was also not indicated.

Two hundred and eighty-one patients in the unrestricted efficacy population had a median PFS of [redacted] months (95% CI: [redacted]). A total of 175 patients [redacted]) in this population were censored for analysis and [redacted] patients ([redacted]) had a PFS event. [redacted] reported to be [redacted] (treatment-naïve subgroup (n=116): estimated median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored; prior systemic treatment subgroup (n=165): median PFS was [redacted] months (95% CI: [redacted]), with [redacted] of patients censored).

No safety data were provided for any of the comparator treatments considered, so the relative safety and tolerability of pralsetinib cannot be rigorously determined by data from the ARROW trial. As part of the response to clarification the company claimed that there were a number of problems with generating comparative safety data and did not do so. Regardless of whether they are correct, the ERG notes that comparative safety data about pralsetinib is currently unavailable.

The company chose to conduct an individual patient data (IPD) analysis using real-world data, this was prioritised, and the company chose the Flatiron study for the comparison with pembrolizumab plus pemetrexed plus chemotherapy and pembrolizumab monotherapy. In addition, a SLR was conducted to inform the other comparisons in the WT population employing the stepwise process. The ERG noted a number of methodological problems with the SLRs, including baseline differences between these studies. The differences included more females in the GOIRC study as compared with the LUME-Lung 1 trial i.e., 72.3% versus 37%. Only 8% of patients had brain metastases in the LUME-Lung 1 trial versus 37.3% in the ARROW study.[27] Also a ECOG PS of one was the lowest in the GOIRC trial compared with the other three studies. Metastatic disease at baseline was not reported in three trials.[24, 27, 32]

The company undertook a SLR to assess the efficacy and safety of treatment for people with locally advanced or metastatic *RET-positive* NSCLC. A more specific aim was to compare pralsetinib with relevant comparators used in clinical practice. To address the gaps in evidence relating to the comparators of interest, the company performed a second SLR that modified the participant eligibility

criteria to include people with WT NSCLC. The aim of the second SLR was to identify RCTs that evaluated relevant comparator interventions in participants with WT advanced or metastatic NSCLC.

The ERG raised a number of concerns regarding the two SLRs (SLR 1, and SLR 2).

1. There was an unexplained difference in the inclusion criteria between the two SLRs. SLR 1 included a range of clinical trial, non-randomised and observational study designs. SLR 2 included only phase I, II or III RCTs or extension phases of RCTs, and excludes non-randomised experimental and observational study designs. The reason for this discrepancy is not explained, and the exclusion of non-randomised and observational study designs from SLR 2 a cause for concern because of the potential omission of data on safety outcomes.
2. The NICE final scope describes a series of comparators, stratified according to untreated disease/previously treated disease, tumour histology and biomarker status. The same comparators are shown in Table 3 (the decision problem) of Document B. Some of these comparators were omitted in the evidence presented by the company.
3. The specific, eligible comparators for the first SLR (SLR 1) were not clear from the stated study eligibility criteria, making the extent to which the selection of comparators reflect current practice in the UK NHS.
4. SLR 1 and SLR 2 measured different outcomes, with SLR 2 omitting response rate and some of the safety outcomes mentioned in SLR 1.

Systematic literature review 1 identified 46 publications of 38 unique studies articles for inclusion in their SLR. The included studies were retrospective, case-series, or open-label phase I/II.

Systematic literature review 2 included 131 unique studies related to one of the seven interventions of interest.

Due to the gaps in the evidence, the company did not conduct the planned MAIC of pralsetinib versus other treatments for patients with *RET*+ NSCLC (SLR 1).

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

The same SLR searches performed to identify clinical effectiveness evidence were used to identify cost effectiveness studies, HRQoL studies and costs and healthcare resource use studies (CS Appendices G, H and I).

4.1.1 Searches performed for cost effectiveness section

Appendices G, H and I of the CS reported the literature searches used to identify cost effectiveness studies, HRQoL studies and costs and healthcare resource use studies. The searches were conducted in October 2020. A summary of resources searched is provided in Table 4.1 of the critique of the methods of the clinical efficacy and safety review (3.1). The Evidence Review Group comments on the literature searches are provided in Section 3.1.1.

Additional sources searched for the cost effectiveness review, HRQoL review, and costs and healthcare resource use review are summarised in Table 4.1.

Table 4.1: Additional sources searched for cost effectiveness studies, HRQoL studies, and costs and healthcare resource use

Search strategy element	Resource	Host/Source	Date Range	Date searched
Additional sources: cost effectiveness	CEA Registry	www.cearegistry.org	Not reported	Not reported
	RePEc	http://repec.org/	Not reported	Not reported
	NIHR	https://www.journalslibrary.nihr.ac.uk/	Not reported	Not reported
	INAHTA	http://www.inahta.org/	Not reported	Not reported
	University of York CRD	https://www.crd.york.ac.uk/CRDWeb/	Not reported	Not reported
Additional sources: HRQoL	EuroQoL website	https://euroqol.org/	Not reported	Not reported
	SCHARRHUD	https://www.scharrhud.org/	Not reported	Not reported
	NIHR	https://www.journalslibrary.nihr.ac.uk/	Not reported	Not reported
	INAHTA	http://www.inahta.org/	Not reported	Not reported
	University of York CRD	https://www.crd.york.ac.uk/CRDWeb/	Not reported	Not reported
Additional sources: costs and resource use	RePEc	http://repec.org/	Not reported	Not reported
	NIHR	https://www.journalslibrary.nihr.ac.uk/	Not reported	Not reported
	INAHTA	http://www.inahta.org/	Not reported	Not reported

	University of York CRD	https://www.crd.york.ac.uk/CRDWeb/	Not reported	Not reported

CEA Registry = Cost-Effectiveness Analysis Registry; CRD = Centre for Reviews and Dissemination; HRQoL = health-related quality of life; RePEc = Research Papers in Economics; NIHR = National Institute for Health research; INAHTA = International Network of Agencies for Health Technology Assessment; SCHARRHUD = University of Sheffield SCHARRHUD utility database

ERG comment:

- See ERG comments in Section 3.1.1.
- A number of useful additional sources were searched for each of the economic related sections, but details of the search terms used, dates of searches, and results were not reported in the CS. Full details of these searches were provided in response to the ERG clarification letter.
- Health-state unit costs and resource use data were derived from previous NICE technology appraisals, NHS reference costs and unit costs of health and social care.[38, 39]

4.1.2 Inclusion/exclusion criteria

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

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with stage III/IV RET+ NSCLC, regardless of treatment line	• Paediatric patients • Patients with NSCLC who are not RET+ • Mixed populations (where a breakdown of data for patients with RET+ disease is not provided)
Intervention & comparators	Pharmacological interventions for NSCLC (For HRQoL and cost studies: no restrictions)	• Non-pharmacological interventions (e.g., surgery, radiotherapy) • Diagnostic interventions (e.g., screening)
Outcomes(s) 1 (Published economic evaluations)	• Summary costs and health outcomes (e.g., QALYs, LYG) • Cost effectiveness estimates (e.g., ICERs) • Assumptions underpinning analysis • Model structure and summary (including perspective, time horizon, and discounting) • Methods of extrapolation (OS, PFS)	Outcomes not listed in "include" column
Outcomes(s) 2 (HRQoL studies)	• HSUVs (and disutilities (e.g., associated with progression or AEs)) for relevant health states	Outcomes not listed in "include" column

	Inclusion criteria	Exclusion criteria
	(individual (patient or caregiver)) derived using the following techniques: a) Generic, preference-based instruments (e.g., EQ-5D [3L/5L], SF-6D, HUI2, HUI3, AQoL, 15D, QWB, MAUI) b) Direct methods (e.g., TTO, SG, VAS) c) Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs • Disease-specific/generic (non-utility) HRQoL data (e.g., EORTC-QLQ-C30)	
Outcomes(s) 3 (Cost/resource use studies)	• Direct costs: Medical (e.g., medications, staff, hospitalisations, management of AEs) and non-medical (e.g., travel, childcare) • Indirect costs • Cost drivers • Healthcare resource use	Outcomes not listed in "include" column
Study design 1 (Cost effectiveness analysis studies)	• Cost effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis	• Reviews/editorials • BIMs • Case reports • Pharmacokinetic studies • Animal/in vitro studies
Study design 2 (HRQoL studies)	• Studies reporting original HSUV data	• Reviews/editorials • BIMs • Case reports • Pharmacokinetic studies • Animal/in vitro studies
Study design 3 (Cost/resource use studies)	• Studies reporting original cost/resource use data	• Reviews/editorials • BIMs • Case reports • Pharmacokinetic studies • Animal/in vitro studies
Geography	No restriction	
Publication date	No restriction	
Language	English language publications or non-English language publications with an English abstract	Non-English language publications without an English abstract

	Inclusion criteria	Exclusion criteria
Source: Tables 15, 21, and 29 of Appendix G, H and I respectively[28] AEs = adverse events; EORTC = European Organisation for Research and Treatment of Cancer; ICER = incremental cost effectiveness ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; QLQ-C30 = quality of life questionnaire; RET+ = rearranged during transfection positive		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined inclusion and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

No published economic evaluations were identified for final inclusion in the economic evaluation SLR.

ERG comment:

- A comprehensive selection of databases and resources were searched, and the searches were transparent and reproducible. The same SLR searches performed to identify clinical effectiveness evidence were used to identify cost effectiveness studies, HRQoL studies and costs and healthcare resource use studies. Overall, the ERG does not have any major concerns regarding the searches.
- A number of potential problems were raised about the eligibility criteria for the SLRs (see section 3.1.1).

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

4.2.1 NICE reference case checklist

The NICE reference case checklist is provided in Table 4.3 below.

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients included
Perspective on costs	NHS and PSS	NHS and PSS
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Cost utility analysis with pairwise comparisons, no fully incremental analyses provided
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The time horizon of 25 years is considered sufficient to capture relevant differences in cost and outcomes
Synthesis of evidence on health effects	Based on systematic review	Systematic review performed to identify additional evidence on health effects beyond trial data. However, none of the studies found pertained to RET fusion positive NSCLC.

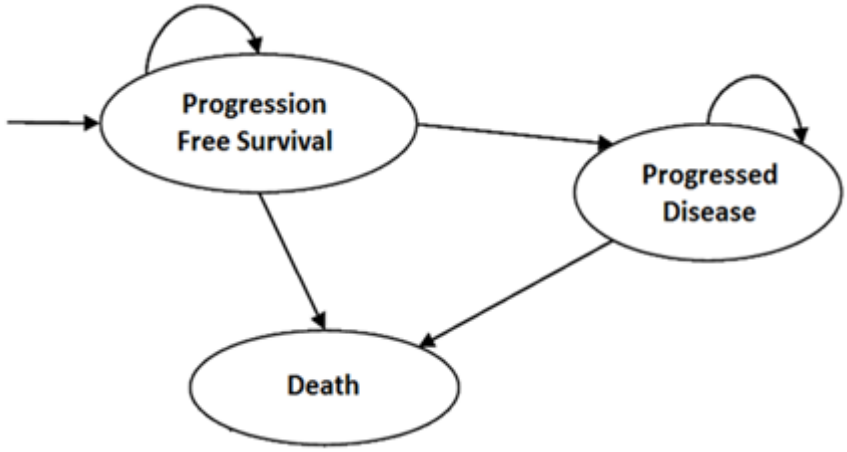
Element of HTA	Reference case	ERG comment on company's submission
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects were expressed in QALYs based on EQ-5D
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	EQ-5D was not collected in ARROW so HRQoL values were based on previous STAs
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity issues have been identified
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	The model includes the costs that relate to NHS and PSS resources, valued using the prices relevant to the NHS and PSS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects were both discounted at 3.5%

ERG = Evidence Review Group; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NSCLC = non-small cell lung cancer; QALY = quality adjusted life year; RET = rearranged during transfection; STA = single technology appraisal; UK = United Kingdom

4.2.2 Model structure

A partitioned survival model was used in the economic analysis. The model was developed in Microsoft Excel. The model included three mutually exclusive health states: "progression-free (PF)", "progressed disease (PD)" and "death". All patients enter the model in the PF health state and remain in this health state until they progress. Upon progression, patients either transition into the PD health state or enter the absorbing health state of death. Patients in the PD health state stay in that health state until death. Patients cannot transition to an improved health state. Figure 4.1 shows the model structure.

Figure 4.1: Economic model structure



Source: Based on Figure 31 of the CS

ERG comment:

- The company has performed the economic analysis using a partitioned survival model. Ideally, the results would be verified by a different type of mode, such as a state transition model.
- One potential issue with partitioned survival models is that PFS and TTD can potentially exceed OS when independently sampled. Upon inspection of the model implementation, the ERG concluded that this issue was not dealt with properly and had a significant impact on the outcomes produced by the probabilistic sensitivity analysis. The ERG raised this issue in the clarification letter under clarification question C15. In their response to clarification, the company claimed to have resolved this issue in an updated version of the model, however, upon close inspection of the updated model it became apparent that the issue persisted. Therefore, the ERG has implemented a modification in the updated model using optional constraints, applied to both the PFS and TTD implementations, to ensure that model calculations can be completed without PFS and TTD exceeding the OS.

4.2.3 Population

The patient population included in the economic evaluation consisted of adult patients with *RET* fusion-positive advanced NSCLC not previously treated with a *RET* inhibitor. The company has submitted economic analyses in both untreated and pre-treated populations, but also stated that the untreated population is the primary focus of the appraisal given the higher degree of unmet need in this population. The company stated that the economic evaluation was in line with the proposed marketing authorisation and the NICE final scope. The proposed marketing authorisation is line-agnostic, meaning patients are eligible to be treated with pralsetinib in all lines of treatment. The main body of clinical evidence for pralsetinib was derived from ARROW, which included both untreated and pre-treated *RET* fusion-positive NSCLC subjects, among other disease types.[2]

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

	Mean (SD) (%)	Source
Mean age of population at baseline	63	Table 8, CS
% males	52%	Table 8, CS
Mean BSA, m^2	1.75	BLU-667 CSR; Table 14, Demographics (Safety population) [2]
Mean weight, kg	65.50	Not reported (but not used in model as dosing based on BSA)

Source: Based on Table 8 of the CS and the company model
BSA = body surface area; CS = company submission; SD = stable disease; % = percentage

ERG comment: The population in the economic evaluation is not fully in line with the NICE final scope. The company did not include pre-treated patients with a RET inhibitor in the economic evaluation while these patients were included in ARROW (Group 6) and the NICE final scope. Since marketing authorisation is line-agnostic, this group should be included in the economic evaluation or excluded from the market authorisation. Moreover, it is not clear how the company excluded these patients for the model inputs such as clinical effectiveness, AEs, costs and HRQoL.

4.2.4 Interventions and comparators

The intervention considered in the CS was pralsetinib, administered orally at a dose of 400 mg QD until disease progression or unacceptable toxicity which is consistent with the anticipated licensed indication stating treatment of RET fusion-positive advanced NSCLC in all lines of treatment.

The primary comparator in the untreated analysis is pembrolizumab plus pemetrexed plus chemotherapy with a secondary analysis against pembrolizumab monotherapy. The primary comparator for the pre-treated economic evaluation is docetaxel monotherapy with secondary analyses against docetaxel plus nintedanib and an additional analysis provided against platinum-based chemotherapy +/- pemetrexed. The dosing and administration frequencies for comparators were applied in the model in line with their marketing authorisations and UK clinical practice. See also Section 2.3 and Table 2.2.

Notably, the NHS CDF clinical lead[6] commented that, in the pre-treated population, atezolizumab is a relevant comparator to include, while docetaxel plus nintedanib is not.

ERG comment:

- The company is making the assumption that RET fusions are rare in squamous patients and therefore excluded from this appraisal. This is probably reasonable; it may be considered to adjust the current indication to only the non-squamous population.
- The ERG was concerned about the exclusion of atezolizumab in the pre-treated population. The NHS CDF clinical lead advised that atezolizumab is a relevant comparator to 2L pralsetinib whereby patients received 1L platin plus pemetrexed. The current appraisal may therefore not be reflective of UK clinical practice. The ERG was unable however to evaluate the potential impact of this exclusion on cost effectiveness. See also Section 2.3.
- Despite the fact that docetaxel plus nintedanib was listed in the NICE final scope, the NHS CDF clinical lead stated that nintedanib is not used much as it has unpleasant toxicities and adds very little benefit. Therefore, the ERG considers the comparison with docetaxel plus nintedanib to be less relevant than the other comparisons in this appraisal.

4.2.5 Perspective, time horizon and discounting

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

ERG comment: Perspective and discounting are appropriate. The half-cycle correction partly compensates for the loss of resolution of the 1 month cycle time compared to a 1 week cycle time for comparable appraisals, as for instance in ID3743.[40]

4.2.6 Treatment effectiveness and extrapolation

The primary source for clinical data for pralsetinib in the economic model is the ARROW study. ARROW is a phase I/II, global, single-arm, open-label, multicentre study in patients with *RET* fusion–positive NSCLC and other advanced solid tumours. Overall survival and PFS were secondary efficacy endpoints in Phase 2 of the ARROW study. The current submission modelled pralsetinib based on the unrestricted efficacy population, which included all *RET* fusion–positive NSCLC patients who were initiated with 400 mg QD pralsetinib, with a 6 November 2020 data cut. The CS distinguishes between two sub-sets within this unrestricted efficacy population: an untreated sub-group and a pre-treated sub-group.

For pralsetinib, OS, PFS and TTD results from ARROW were extrapolated to the time-horizon of the model as lifetime results are not available for subjects in the ARROW study. Guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19 was followed to identify base-case parametric survival models for OS, PFS and TTD.[41] The six parametric distributions used in the analyses were the exponential, Weibull, log-normal, generalised gamma, log-logistic, and Gompertz distributions. All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data, however, when extrapolations had a narrow statistical difference, visual inspection and clinical plausibility were paramount in choosing the base-case parametric model.

Given the immaturity of the data, a large proportion of OS across the model time horizon was measured by the extrapolated part of the curve. Given the importance of the extrapolated period to model survival, a key factor in curve selection was long-term clinical plausibility in the extrapolated period. In order to inform long-term clinical plausibility of parametric models and to determine the OS curve selection used in the model base-case, an advisory board was held.[9] Clinical experts were asked to predict plausible ranges for OS, PFS and TTD for pralsetinib and comparators at landmark survival periods. Following this, clinicians were shown extrapolations and asked to confirm which were and were not plausible.

As no comparators were included in ARROW, an indirect treatment comparison was conducted to estimate relative effectiveness. The indirect and mixed treatment comparisons were described in section B.2.9 of the CS. Initially, a SLR was conducted for a matching adjusted indirect comparison to inform decision making. See appendix D of the CS.[28] No studies were identified that corresponded to the comparators identified in Section B.1.1 of the CS, so a MAIC in this patient population was not a feasible approach. Subsequently, real world evidence was used in order to inform an indirect treatment comparison. A treatment comparison between RET fusion-positive NSCLC patients treated with pralsetinib from the ARROW clinical trial versus best available therapy for RET fusion-positive advanced NSCLC in the Flatiron database failed due to sample size limitations. The company conducted a chart review, but at the moment of writing the ERG report this was still ongoing. In the absence of available evidence to inform a *RET* fusion-positive comparison, an approach was taken to conduct an

indirect treatment comparison of pralsetinib data from ARROW against a WT population from the available literature, which resulted in hazard ratios for the comparators for the pre-treated sub-group. For the untreated sub-group, an indirect treatment comparison was conducted based on a propensity score analysis using IPTW methodology, performed on patient level data extracted from the Flatiron database.[30]

Overall survival, PFS, and TTD for comparators were estimated by applying the hazard ratios from the indirect treatment comparison to the pralsetinib arm using hazard ratios as shown in Table 4.5. Given that an indirect treatment comparison was used, proportional hazard between pralsetinib and comparators was assumed and therefore distributions which support the proportional hazards assumption were preferred for modelling survival.

Table 4.5: Summary of HRs vs. pralsetinib used in the indirect treatment comparison and source of comparator data

Treatment	OS HR (95% CIs)	PFS HR (95% CIs)	TTD HR (95% CIs)	Source
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (PSW ATT)[30]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	Flatiron Health EDM dataset (PSW ATT)[30]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	OAK trial (propensity score weighting ATT; TTD assumed equal to PFS) [13, 42]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	LUME-Lung 1 (naïve comparison; PFS and TTD assumed equal to docetaxel monotherapy)[33]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	GOIRC 02-2006 + NVALT7 (naïve comparison; TTD assumed equal to PFS)[24]

Source: Table 35 of the CS[1]
CS = company submission; EDM = Enhanced Data Mart; HR = hazard ratio; OS = overall survival; PFS = progression free survival; PSW = propensity score weighting; TTD = time to treatment discontinuation

4.2.6.1 Untreated sub-group

For the analyses with the untreated sub-group, the comparators used were pembrolizumab plus pemetrexed plus chemotherapy and pembrolizumab monotherapy. Hazard ratios were estimated from a comparison of untreated pralsetinib patients in ARROW to untreated advanced WT NSCLC patients receiving the comparator in the US Flatiron Health dataset. Patients in comparator arms were adjusted using propensity score matching based on baseline characteristics to ARROW patients to adjust for differing characteristics of RET fusion-positive patients.

4.2.6.2 Untreated sub-group: OS extrapolation

The six parametric distributions were fitted to the observed pralsetinib untreated OS data. Although, based on AIC and BIC, the best fitting parametric model was the exponential curve, the Weibull distribution was selected for modelling pralsetinib OS as clinical experts suggested that its characteristic decreasing hazard function over time was observed in this patient population.

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib OS.

Although the Weibull and exponential distributions represented the most conservative extrapolations and best represented the clinical experts' plausible landmark survival predictions for pralsetinib, both distributions substantially underpredicted the clinical experts' plausible landmark survival predictions for the comparators (see Table 4.6).

Table 4.6: Validation for model untreated OS at various time points

	3 years			5 years			10 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
EO	50%	30%	25%	40%	10%	8%	10%	3-5%	2%
Weibull*	[redacted]								
Exponential	[redacted]								
GG	[redacted]								
Gompertz	[redacted]								
Log-logistic	[redacted]								
Log-normal	[redacted]								

Source: Based on Table 39 of the CS
CS = company submission; EO = expert opinion; GG = generalised gamma; OS = overall survival
*Base-case selection

4.2.6.3 Untreated sub-group: PFS extrapolation

The six parametric distributions were fitted to the observed pralsetinib untreated PFS data. Although, based on AIC and BIC, the best fitting parametric model for PFS was the log-normal curve, the exponential distribution was selected as it was deemed by the clinical experts as the most realistic distribution to model long-term PFS for pralsetinib and comparators (see Table 4.7).

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib PFS.

Table 4.7: Validation for model untreated PFS at various time points

	3 years			5 years			10 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
EO	30-35%	15%	5%	10-15%	5%	1%	5%	1%	0-1%
Weibull	[redacted]								
Exponential*	[redacted]								
GG	[redacted]								
Gompertz	[redacted]								

	3 years			5 years			10 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 42 of the CS
CS = company submission; EO = expert opinion; GG = generalised gamma; PFS = progression free survival
*Base-case selection

4.2.6.4 Untreated sub-group: TTD extrapolation

The six parametric distributions were fitted to the observed pralsetinib untreated TTD data. For pralsetinib, a similar trend to PFS was assumed. Based on AIC and BIC, the best fitting parametric model for PFS was the exponential curve and was selected as it was both recommended by the clinical experts and maintained consistency with the curve choice for PFS (see Table 4.8).

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison. To reflect UK practice, a stopping rule on pembrolizumab treatment regimens at 2 years was implemented in the model.

Table 4.8: Validation for model untreated TTD at various time points

	3 years			5 years			10 years		
	Pral.	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**	**Pral.**	**Pemb + chem.**	**Pemb. mono**
EO	30-35%	0%	0%	10-15%	0%	0%	5%	0%	0%
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 45 of the CS
CS = company submission; EO = expert opinion; GG = generalised gamma; TTD = time to treatment discontinuation
*Base-case selection

4.2.6.5 Pre-treated sub-group

For the analyses with the pre-treated sub-group, the comparators used were docetaxel monotherapy, docetaxel plus nintedanib, pemetrexed plus platinum-based chemotherapy, and platinum-based chemotherapy. Hazard ratios were estimated from comparing pre-treated pralsetinib patients in ARROW to available published studies of WT advanced NSCLC patients. Patients in the comparator arms were adjusted based on baseline characteristics to ARROW patients to adjust for differing characteristics of RET fusion-positive patients where possible.

4.2.6.6 Pre-treated sub-group: OS extrapolation

The six parametric distributions were fitted to the observed pralsetinib pre-treated OS data. Although, based on AIC and BIC, the best fitting parametric model for PFS was the generalised gamma curve, the exponential distribution was selected. The exponential curve over-predicts the clinical expert's landmark OS prediction at 3 years, but slightly under-predicts OS in the ARROW trial at 2 years and aligns with the clinical experts' expectation of median OS for docetaxel monotherapy in this population from the selpercatinib appraisal (see Table 4.9).

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib OS. Clinical experts agreed that they did not expect to see a notable difference in OS between docetaxel monotherapy and docetaxel plus nintedanib patients.

Table 4.9: Validation for model pre-treated OS at various time points

	3 years				5 years				10 years			
	Pra	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**
EO	35%	5%	5%	15%	20%	2%	2%	5%	7%	0%	0%	1%
Weibull	[redacted]											
Exponential*	[redacted]											
GG	[redacted]											
Gompertz	[redacted]											
Log-logistic	[redacted]											
Log-normal	[redacted]											

Source: Based on Table 48 of the CS
CS = company submission; EO = expert opinion; GG = generalised gamma; OS = overall survival; Pra = pralsetinib; DoM = docetaxel monotherapy; DoN = docetaxel plus nintedanib; PBC +/- pem = pemetrexed +/- platinum-based chemotherapy
*Base-case selection

4.2.6.7 Pre-treated sub-group: PFS extrapolation

The six parametric distributions were fitted to the observed pralsetinib pre-treated PFS data. Although, based on AIC and BIC, the best fitting parametric model for PFS was the generalised gamma curve, clinical experts suggested that the generalised gamma distribution was not clinically plausible and therefore the exponential distribution was selected as the most clinically plausible curve (see Table 4.10).

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib PFS.

Table 4.10: Validation for model pre-treated PFS at various time points

	3 years				5 years				10 years			
	Pra	DoM	DoN	PBC +/- pem	Pra	DoM	DoN	PBC +/- pem	Pra	DoM	DoN	PBC +/- pem
EO	30-35%	1-2%	1-2%	5%	10-15%	0%	0%	1%	5%	0%	0%	0%

	3 years				5 years				10 years			
	Pra	DoM	DoN	PBC +/- pem	Pra	DoM	DoN	PBC +/- pem	Pra	DoM	DoN	PBC +/- pem
Weibull	[redacted]											
Exponential*	[redacted]											
GG	[redacted]											
Gompertz	[redacted]											
Log-logistic	[redacted]											
Log-normal	[redacted]											

Source: Based on Table 51 of the CS

CS = company submission; EO = expert opinion; GG = generalised gamma; PFS = progression free survival; Pra = pralsetinib; DoM = docetaxel monotherapy; DoN = docetaxel plus nintedanib; PBC +/- pem = pemetrexed +/- platinum-based chemotherapy; * = Base-case selection

4.2.6.8 Pre-treated sub-group: TTD extrapolation

The six parametric distributions were fitted to the observed pralsetinib pre-treated TTD data. Although, based on AIC and BIC, the best fitting parametric model for PFS was the log-normal curve, the log-normal curve was thought to over predict long-term TTD substantially and based on clinically plausible landmark TTD the exponential distribution was selected as the most clinically plausible curve. In addition, exponential distribution maintains consistency with the PFS choice (see Table 4.11).

The comparators were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib TTD. In studies from the published literature, TTD was not reported and therefore it was not possible to calculate a hazard ratio. Therefore, an assumption was made that the hazard ratio on TTD was equal for the hazard ratio for PFS for pralsetinib versus each comparator respectively.

Table 4.11: Validation for model pre-treated TTD at various time points

	3 years				5 years				10 years			
	Pra	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**
EO	30-35%	0%	0%	1%	10-15%	0%	0%	0%	5%	0%	0%	0%
Weibull	[redacted]											
Exponential*	[redacted]											
GG	[redacted]											
Gompertz	[redacted]											
Log-logistic	[redacted]											
Log-normal	[redacted]											

Source: Based on Table 54 of the CS

	3 years				5 years				10 years			
	Pra	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**	**Pra**	**DoM**	**DoN**	**PBC +/- pem**
CS = company submission; EO = expert opinion; GG = generalised gamma; Pra = pralsetinib; DoM = docetaxel monotherapy; DoN = docetaxel plus nintedanib; PBC +/- pem = pemetrexed +/- platinum-based chemotherapy; TTD = time to treatment discontinuation *Base-case selection												

4.2.6.9 Scenario analyses

Alternative curve choices were investigated in the scenario analysis. For untreated pralsetinib OS, the Weibull distribution was replaced by the exponential distribution in the sensitivity analysis. For untreated pralsetinib PFS and TTD, and pre-treated pralsetinib OS, PFS, and TTD, the exponential distribution was replaced by the Weibull distribution in the sensitivity analysis. Additional curve choices were evaluated and their impact on ICERS for pralsetinib versus comparators were presented in Tables 40 to 42 of the company's response to clarification.[3]

Varying assumptions for hazard ratios are explored in the sensitivity analysis. Four different scenario analyses were conducted for the comparators of the untreated population. One scenario analysis was conducted for the comparators of the pre-treated population. These scenario analyses are listed in Table 5.5.

4.2.6.10 Sensitivity analyses

Parametric uncertainty around the pralsetinib OS, PFS, and TTD curves was evaluated using random multivariate normal draws and a cholesky decomposition. Parametric uncertainty around the hazard ratios for the comparators was calculated using random log-normal draws from corresponding confidence intervals. An overview is presented in Table 71 in the CS.

4.2.6.11 Treatment waning

No assumptions around the potential waning of treatment effects were mentioned in the CS. No option to account for waning treatment effects was included in the model file, as the current implementation in the model assumes constant treatment effects.

ERG comment: The main concerns of the ERG relate to:

- Justification of curve choices. Due to the immaturity of the data and small differences in fit related statistics, curve choices were mainly based on expert advice, and comparisons to landmark survival predictions by experts. Both hazard rates for pralsetinib and hazard ratios for comparators were based on the immature available data. However, due to the similar fit between pralsetinib survival curves on the limited available data, base-case and scenario curves for extrapolation were not chosen based on best statistical fit. Instead, curve choices were made using available landmark predictions provided by [clinical] experts, as shown in Tables 4.6 to 4.11. Although some of the curve choices are on the conservative side for pralsetinib, the underprediction for comparator curves was often even larger, both in absolute and relative terms. For instance, for the untreated subgroup OS the Weibull curve was chosen for pralsetinib (see Table 4.6), and at the 3 years landmark this curve (55%) exceeds the predicted pralsetinib overall survival (50%) by five percentage points (10% relative overprediction), while the comparator curves (19% and 16%) underpredict the predicted landmark survival (30% and 25%) by 11 and nine percentage points (36.7% and 36% relative underprediction). Similarly, at the 5 years and 10 years landmark predictions, the (relative)

underprediction of comparator OS extrapolations is larger than for pralsetinib extrapolations. We observe similar trends with some of the other curve selections. However, as it was difficult to identify curves that were optimal for both pralsetinib and comparators, in particular for the untreated population, the ERG refrains from replacing the distributions in the ERG preferred assumptions. In a scenario, the ERG applied an alternative set of hazard ratios that were calibrated on the expert opinion landmark estimates at 3 years. These hazard ratios reflect OS and PFS survival curves for the comparators that would make a better fit to what the clinicians expected, given original curve choice for pralsetinib. This calibration of hazard ratios reduces the substantial underprediction of the comparator survival curves.

- The absence of a treatment waning effect. No assumptions around the potential waning of treatment effects were mentioned in the CS. No option to account for waning treatment effects was included in the model file, as the company implementation in the model assumes constant treatment effects. Since the hazard ratios applied by the company were based on small sample size and immature data, in particular for the untreated population which was a smaller group in ARROW and had a median follow-up of 9.5 months, a constant and unending treatment effect seems unrealistic. Also, the company did not provide any justification or expert opinion for this assumption other than the landmark estimates which were largely neglected for the comparator extrapolations (see the point above). The ERG is concerned that assuming constant treatment benefits will lead to overly optimistic results for the untreated population in particular, given immaturity of data. To allow for treatment waning in the model, the ERG implemented a feature in the ERG model file which allows for treatment waning through the assumption that hazard ratios to model OS become equal to one over time. Both the time until start of treatment waning and the duration of the treatment waning period (both in years) were implemented as variable parameters for this added model feature. Although this approach may not be ideal as it adjusts comparator OS and not OS for pralsetinib, the ERG believes that in terms of relative cost effectiveness, it is an approximation of actual waning of treatment effect.
- Time on treatment falling below PFS for pralsetinib in the untreated population. The ERG noted a substantial difference between KM data for total time on treatment and PFS in the untreated population, see Figure 4.1. This difference was not present in the pre-treated population, see Figure 4.2. Apparently, in the untreated population after around 12 months, patients were taken off treatment at an increased rate, and not necessarily because of progression. The ERG considered two potential explanations for this observation: 1) an artefact in the data because of small sample size and immaturity or 2) patients were indeed taken off treatment before progression because of an implicit stopping rule. When 1) the difference would be caused by an artefact in the data, this underlines the substantial uncertainty in the tails of the KM curves and therefore in the extrapolation curves fitted to these data. Total time on treatment (and therefore treatment costs) for pralsetinib may have been underestimated in this case. The ERG implemented a scenario where time on treatment is set equal to PFS for all treatment arms, to test the robustness of the model outcomes for uncertainty in time on treatment in the data. When 2) there would indeed be a trend towards stopping treatment before progression, the ERG would be concerned whether the hazard ratios now implemented in the model properly reflect the consequences of the shorter time on treatment as these will probably only become visible in the near future (not yet observed in PFS and OS in current data). Which would in turn make the assumption of a constant treatment benefit more unlikely (related to point b above).

Figure 4.2: Total time on treatment versus PFS – untreated population

Source: reproduced from company model

Figure 4.3: Total time on treatment versus PFS – pre-treated population

Source: reproduced from company model

4.2.7 Adverse events

The main source of evidence on treatment AEs used for pralsetinib was the ARROW safety population,[2] using the ITT population which contained subjects not exclusive to NSCLC and subjects on all doses (n=404). Adverse events for comparators were taken from the available literature for the respective treatment. All grade ≥ 3 events with an incidence of ≥ 2% in at least one treatment arm were included in the economic model. From the clinical study report it was apparent that it was treatment-emergent (all) AEs that were included for pralsetinib, and not only treatment-related AEs.[2]

ERG comment: The main concerns of the ERGs relate to:

- Inconsistent sample size of safety population and AE incidence rates between Sections B.2.10 and B.3.3.3 of the CS. In the clinical sections of the submission (B.2.10), AEs for a sample of 528 were reported, while in the health economic sections (B.3.3.3), and in line with the CSR, a sample size of 404 is mentioned. For those grade ≥3 AEs reported in Table 28 of the CS, incidences are slightly higher than in Table 55. For instance, the percentage of anaemia cases was 17.2% in Table 28 compared to [redacted] in Table 55. The latter (lower) incidence was implemented in the model. See Table 4.12 for more details. As the CSR and Section B.2.10 of the CS only reported on AEs with ≥10% incidence, not all AEs included in the model were reported there so the comparison can only be made for the four AEs in this Table.

- Several inconsistencies in the AE incidences used for the comparators. For the pembrolizumab monotherapy comparator in the untreated population, a study by Mok et al. was used,[43] which led to a 7% rate for pneumonia in Table 55 of the CS, while all other AEs were set to zero. In the referenced source, pneumonia was not listed as one of the AEs though. Pneumonitis was, at a rate of 4% but this was set to 0% for the model. For the pre-treated population, the source provided for the AE incidences with docetaxel monotherapy, Mazieres et al.,[42] did not contain information on individual AEs for docetaxel, and sample size deviated as well. For the PBC +/- pembrolizumab comparator, AE rates were taken from Ardizzoni et al. [24] with a sample size of 287 according to Table 55 of the CS, but the study population reported in the paper consisted of 229 patients. Also, the AE rates reported in this paper do not align very well with Table 55 of the CS (for instance, 16 cases of anaemia in the study versus zero in the CS, and 14 cases of fatigue in the study versus nine in the model). The company may have done recalculations or additional assumptions which cause these differences, but none of this was provided in the CS.

Summarising, although the ERG considers the way AE incidence was included in the model to be justified, the actual incidences used may be subject to error in both the pralsetinib and comparator arms which can be a source of bias. Although the ARROW safety population was slightly broader than the population included in the economic model, it was apparent from the CSR that AE incidence was essentially no different between the separate subpopulations. Also, using treatment-emergent AEs can be regarded a conservative approach.

Table 4.12: AE incidences reported in clinical study report versus CS

	All patients, 400 mg QD		All patients, all doses/schedules
Preferred term, n (%)	**Table 37 CSR (n=354)**	**Table 28 CS (n=528)**	**Table 37 CSR (n=404)**
Patients with any Grade ≥3 AE	232 (65.5)	406 (76.9)	274 (67.8)
Anaemia	43 (12.1)	91 (17.2)	52 (12.9)
Hypertension	49 (13.8)	85 (16.1)	57 (14.1)
Neutropenia	37 (10.5)	59 (11.2)	42 (10.4)
Neutrophil count decreased	NA*	51 (9.7)	20 (5)*

Source: Table 37 of the CSR and Table 28 of the CS
AE = adverse event; CS = company submission; n = number of people treated; QD = once daily; % = percentage
*Table 37 of the CSR did not contain an incidence for decreased neutrophil count, as only AEs with ≥10% incidence was reported here. The number in the last column was therefore taken from Table 55 of the submission which contained AE incidences as used in the model and applied to the n=404 safety population.

4.2.8 Health-related quality of life

The utility values were estimated separately for the untreated and pre-treated populations, and for the following health states: progression free and progressed disease. The company did not administer the EuroQoL-5D within ARROW. Instead, EORTC QLQ-C30 data were collected to obtain HRQoL data directly from RET fusion-positive NSCLC subjects. The company attempted to map EORTC QLQ-30 onto EQ-5D-3L but considered these mapped estimates not robust enough to inform decision making because of the large amount of missing data. Utility values used to inform the model were then sourced from previous STAs in advanced NSCLC which were identified by handsearching. Disutilities were assigned for AEs, and also a correction for age and sex was applied.

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

According to the CS, the SLR did not identify any studies which reported utility data associated specifically with patients with RET fusion-positive NSCLC. Therefore, previous NICE appraisals were hand searched in order to identify relevant health state utility values to inform the economic model.

4.2.8.2 Health state utility values

The health state utility values used to inform the economic model were derived from previous STAs which were identified by handsearching. For both the untreated and pre-treated population, three different sources were used (one for base-case, two others for scenarios). For the pre-treated population the company justifies in the CS that given the similarities between the current appraisal and the ongoing ID3743, the utilities as used in ID3743 were used in the base-case.[40] For the untreated population however, there is no explanation on choice for base-case, and all three sources may be equally applicable to the current appraisal.

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.13.

Table 4.13: Health state utility values

Health state	Utility PF	Utility PD	Reference	Justification
Untreated				
TA654 (base-case)	0.794	0.678	[44]	EGFR-positive suitable proxy for RET fusion-positive given similarities between patient populations
TA310 (scenario)	0.784	0.725	[45]	ALK-positive suitable proxy for RET fusion-positive given similarities between patient populations
TA643 (scenario)	0.780	0.660	[46]	ROS1-positive suitable proxy for RET fusion-positive given similarities between patient populations
Pre-treated				
TA713, ID3743 (base-case)	0.713	0.628	[40, 47]	Advanced NSCLC considered suitable proxy for RET fusion-positive given similarities between patient populations
TA653 (scenario)	0.853	0.659	[48]	EGFR-positive suitable proxy for RET fusion-positive given similarities between patient populations
TA310 (scenario)	0.672	0.653	[45]	ALK-positive suitable proxy for RET fusion-positive given similarities between patient populations

Source: Table 56 of the CS[1]
ALK = anaplastic lymphoma kinase; CS = company submission; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD = progressed disease; PF = progression-free; RET = rearranged during transfection

4.2.8.3 Disutility values

All grade ≥3 events with an incidence of ≥2% in at least one treatment arm were included in the economic model. Disutilities associated with the AEs were implemented in the model by calculating a QALY loss which was the product of the disutility and the duration of the AE and applied in the first cycle of the model. Disutilities were sourced from available published literature or assumed to be zero, and duration was either derived from previous appraisals, or assumed at a certain value (15 days, or 23.8 days when comparable with fatigue). See Table 57 of the CS.[1] In the clarification phase, the ERG requested to company to provide a scenario where all the zero disutilities were replaced by the disutility for fatigue. The company provided this scenario and ICERs changed only very marginally.

ERG comment: The main concerns of the ERGs relate to:

- The lack of observed HRQoL. Although there were EORTC-QLQ-C30 data from the ARROW trial, the company considered these unfit to inform the economic model. The company therefore chose to use health state utilities from previous STAs. In particular for the untreated population, the ERG was not convinced that the STA chosen to inform the base-case (from an EGFR-positive population) was indeed the most suitable proxy, as the two STAs in the scenarios (ALK and ROS1 positive populations) were also said to be suitable proxies.
- The lack of justification for the difference in health state utilities between the untreated and pre-treated populations. The base-case utilities were substantially higher for the untreated compared to pre-treated population. In the clarification phase, the ERG asked he company to provide a justification for this difference, and also requested the mapped EORTC QLQ-C30 data from ARROW, stratified for population. In their response, the company stated that those being progression-free in the pre-treated population would, in terms of HRQoL, be comparable to those after progression in the untreated population. However, the mapped EORTC QLQ-C30 revealed there was hardly any difference between the two populations, the pre-treated population had a higher mapped utility value even than the untreated population. Since the ARROW data are the only source of evidence that includes both untreated and pre-treated in one dataset, and is RET-positive specific, the ERG is concerned about the validity of the utility scores used in the company base-case, not coming from the same source.
- Choice of health state value for PD in the pre-treated population. The value of 0.628 used in the base-case is debatable, as it was in TA713[47]and ID3743 [40]. In both appraisals, health state utilities were based on TA484 (which was the earlier appraisal for nivolumab now replaced by TA713), except for the PD value which was much lower in TA484. In TA713 the final value agreed on in committee was 0.569 as the values from the clinical study informing the appraisal had increasingly missing values and therefore could be biased by being mostly from healthier patients. In ID3743 there was also discussion, but the final outcome is not yet known at the time of writing this report.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, medical costs (treatment administration, supportive care, terminal care), and costs of managing AEs. Costs of genomic testing were included in a scenario but not in the base-case analysis.

Unit prices were based on the NHS reference prices,[39] British National Formulary (BNF) ,[49] Personal Social Services Research Unit (PSSRU) [38]and the electronic market information tool (eMIT).[50] Unit prices were expressed in or updated to the 2020 price level.

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified one study to be potentially informative but as it was a conference abstract only and not considered relevant to the decision problem or UK clinical practice, it was not used to inform the economic model. Costs and resource use in the economic model were therefore based on available evidence in previous NICE submissions.

4.2.9.2 Treatment costs (with PAS)

Treatment acquisition costs as used in the economic model are summarised in Table 4.14. For regimens including either cisplatin or carboplatin, a 50:50 split of cisplatin and carboplatin was assumed which, according to the company, was in line with clinical expert opinion. No other platinum-based chemotherapies were included in the costings given the minimal impact of drug acquisition costs of platinum-based chemotherapies on model results and cisplatin and carboplatin are the most commonly used. For platinum-based chemotherapy +/- pemetrexed, it was assumed that 63% of patients received pemetrexed. The company stated this to be in line with UK clinical practice and a conservative assumption since in the study that informed the efficacy for platinum-based chemotherapy +/- pemetrexed in the indirect comparison, 100% of patients received pemetrexed.[24]

The text of Section B.3.5 of the CS did not provide information on dosage, potential vial sharing, or relative dose intensity. From the economic model it was apparent though that dosing as provided in Section 4.2.4 (interventions and comparators) of the CS was used, where relevant, in combination with a BSA of 1.75 m^2 taken from the ARROW safety population.[2] Vial sharing was assumed for IV medication, and relative dose intensity was set to one for all drugs, so no dose reductions (or escalations) were implemented.

Table 4.14: Treatment acquisition costs

Line	Regimen	Drug	Pack size	Price per pack (£)	Cost per month (£)	Source
Untreated	Pralsetinib	Pralsetinib (PAS price)	120 x 100mg	[redacted]	[redacted]	--
	Pembrolizumab + pemetrexed + chemotherapy	Pembrolizumab	1 x 100mg	2,630.00	7,623.87	BNF[49]
		Pemetrexed	1 x 100mg	160.00	2,029.17	BNF[49]
		Cisplatin	1 x 100mg	8.73	16.61	eMIT[50]
		Carboplatin	1 x 450mg	13.76	31.02	eMIT[50]
	Pembrolizumab monotherapy	Pembrolizumab	1 x 100mg	2,630.00	7,623.87	BNF[49]
Pre-treated	Pralsetinib	Pralsetinib (PAS price)	120 x 100mg	[redacted]	[redacted]	--
	Docetaxel		1 x 160mg	17.95	21.34	eMIT[50]
	Docetaxel + nintedanib	Docetaxel	1 x 160mg	17.95	21.34	eMIT[50]

Line	Regimen	Drug	Pack size	Price per pack (£)	Cost per month (£)	Source
		Nintedanib	120 x 100mg	2,151.10	2,078.54	BNF[49]
	Platinum-based chemotherapy + /- pemetrexed	Pemetrexed	1 x 100mg	160.00	2,029.17	BNF[49]
		Cisplatin	1 x 100mg	8.73	4.43*	eMIT[50]
		Carboplatin	1 x 450mg	13.76	31.02	eMIT[50]

Source: Table 60 of the CS[1]
BNF = British National Formulary; CS = company submission; eMIT, electronic market information tool; PAS = patient access scheme
*The ERG identified the implemented dosage of cisplatin in the 2nd line to be an error, it was implemented as 20 mg while it should have been 75 mg equal to first line, and therefore also equal costs. The ERG corrected this in their model.

Treatment administration costs are shown in Table 61 of the CS and were dependant on type of administration, but apart from sources that were provided, elaborate justification for the methodology to calculate exact costs was lacking in the CS.

4.2.9.3 Health state and terminal care costs

Health state costs for the PF and PD health states included costs for outpatient and GP visits, contacts with a cancer nurse, blood counts, biochemistry, CT scans, and chest X-rays. The types of resource use and frequency of use were derived from TA643.[46] Resource use was assumed to be equal for the untreated and pre-treated populations. The company stressed that although there is a considerable extra cost burden if a patient progresses in the central nervous system (CNS), which is something pralsetinib may partly prevent, it was not possible to estimate a relative reduction of CNS progression for pralsetinib versus comparators and so this could not be included in the health state costs. Health state costs were assumed to be equal for untreated and pre-treated populations.

Terminal care costs were included for patients who entered the death state as a one-off cost. Terminal care costs included a mix of resource use, such as a district nurse, residential care, and hospital care and was in line with TA643 and a report by Georghiou and Bardsley.[46, 51] See Table 4.15 for an overview of health state and terminal care costs.

Table 4.15: Health state and terminal care costs

Health state	Cost (£)	Source for resource use
Progression free	202.22 per cycle	TA643[46]
Progressed disease	227.01 per cycle	TA643[46]
Terminal care	7,594.42 one-off	TA643 [46, 51]

Source: Tables 62 and 63 of the CS
CS = company submission

4.2.9.4 Event costs

Adverse event unit costs are listed in Table 64 of the CS and were sourced from previous NICE appraisals in NSCLC, or when this was not possible, from the NHS HRG group.[52]The costs of AEs for each treatment arm were then calculated by multiplying the incidence of each AE with its unit cost and

implemented in the economic model as a one-off cost in the first cycle of treatment. See Table 4.16 below for total AE costs per treatment arm.

Table 4.16: Adverse event costs

Line	Regimen	Total adverse event costs (£)
Untreated	Pralsetinib	[redacted]
	Pembrolizumab + pemetrexed + chemotherapy	526.96
	Pembrolizumab monotherapy	48.44
Pre-treated	Pralsetinib	[redacted]
	Docetaxel	240.72
	Docetaxel + nintedanib	315.03
	Platinum-based chemotherapy +/-pemetrexed	245.83

Source: Table 65 of the CS[1]
CS = company submission

4.2.9.5 Subsequent treatment costs

Costs of subsequent treatments were applied as a one-off cost in the economic model when patients enter the PD state. Those patients not receiving a subsequent treatment were assumed to receive best supportive care at no additional cost. The distribution of subsequent treatments was estimated via expert opinion in and advisory board. Treatment duration was estimated from the available published literature. See Table 4.17 for details on distribution and treatment duration for subsequent treatment after first line. Acquisition and administration costs were calculated in a similar way as for first line treatment, leading to total subsequent treatment costs as detailed in Table 4.18.

Table 4.17: Subsequent therapies after treatment discontinuation from first line

	Pralsetinib	Pembro + pemetrexed + chemo	Pembro mono	Treatment duration (months)
Patients who received a subsequent treatment	**69.2%**	**62.8%**	**60.6%**	**--**
Docetaxel	1.5%	23.3%	0.7%	4.1[42]
Docetaxel + nintedanib	1.5%	18.6%	0.7%	4.1[42]
Platinum-based chemotherapy without pemetrexed maintenance	35.9%	20.9%	22.0%	3.5[24]
Platinum-based chemotherapy with pemetrexed maintenance	25.6%	0.0%	37.1%	3.5[24]
Atezolizumab monotherapy	1.5%	0.0%	0.0%	2.8[42]
Nivolumab monotherapy	1.5%	0.0%	0.0%	2.3[47]
Pembrolizumab monotherapy	1.5%	0.0%	0.0%	3.9[53]
Patients who received best supportive care	**30.8%**	**37.2%**	**39.4%**	**--**

	Pralsetinib	Pembro + pemetrexed + chemo	Pembro mono	Treatment duration (months)
Total (all patients)	**100%**	**100%**	**100%**	**--**
Source: Table 66 of the CS CS = company submission Note: subsequent treatment duration for docetaxel plus nintedanib was assumed to be equivalent to docetaxel monotherapy				

Table 4.18: Total subsequent treatment costs per treatment arm

Line	Regimen	Total subsequent treatment costs (£)
Untreated	Pralsetinib	[redacted]
	Pembrolizumab + pemetrexed + chemotherapy	2,649
	Pembrolizumab monotherapy	3,789
Source: Table 69 of the CS CS = company submission		

Following treatment in second line, the company assumed that a high proportion of patients will receive best supportive care and therefore subsequent treatments after second line were not included in the economic model. The ERG requested a scenario including subsequent treatments after second line in the clarification phase which the company did provide. The distribution of the subsequent treatments after second line were derived from ID3743.[40] A minor change in ICERs was observed after implementing the scenario.

4.2.9.10 RET fusion testing costs

As the company stated it to be evident that genomic testing will be implemented for advanced NSCLC patients in the short-term future, costs of RET fusion testing have not been included in the base-case analysis for either untreated or pre-treated analyses.

A scenario analysis was included to explore the potential impact of testing costs on results where patients receiving pralsetinib are assumed to incur a proportion of genomic testing costs representing the potential increase to genomic testing per patient due to pralsetinib in this indication. For this scenario analysis this proportion is arbitrarily assumed to be 10%. Costs of RET fusion testing were estimated in line with TA643[46] at £96.80 per test, which would be £6,453 per RET fusion positive patient (given that 1.5% of the tested population would be RET fusion positive). The amount per RET fusion-positive patient attributable to pralsetinib (10%) would then be [redacted]. This was the cost applied in the scenario.

ERG comment: The main concerns of the ERG relate to:

- A lack of justification for the assumption of health state costs being equal between untreated and pre-treated populations. Given the fact that everything in the model was split up for untreated and pre-treated populations, the ERG wonders why the health state costs were not stratified. By assigning clearly lower health state utility values to the pre-treated population, the company confirmed their view of the pre-treated population being less healthy and therefore it would be expected that also resource use would be higher compared to the untreated population. The resource use was sourced from previous line-agnostic appraisals and so probably the resource use for the untreated population would in reality be slightly lower, and for the pre-treated it may be slightly

higher. Given that health state costs can take up to >20% of total costs (depending on line and comparator), changing resource use could have an impact on the ICER.

- The assumption of 100% RDI for all treatments. In a previous STA, RDI was around 90% for all included treatments as proposed by the company in their submission.[54] In the absence of information on potential dose reductions for treatments involved in this appraisal, the ERG explored a scenario of all RDI for treatment costs set to 90% to demonstrate the impact of potential dose reductions in UK clinical practice to the ICERs.
- A lack of justification for the proportion of 63% pemetrexed in the platinum-based chemotherapy +/- pemetrexed comparator. The company stated the 63% to be in line with UK clinical practice and conservative because in the study that informed the indirect comparison,[42] 100% of patients received pemetrexed. The ERG agrees that 63% may be conservative compared to 100% but as it concerned a study on pemetrexed versus pemetrexed plus carboplatin, it could not have been any less than 100% and this is in no way reflective of UK clinical practice. There is no proper source provided for the 63% and so the ERG is concerned that the 63% may not be conservative.
- The exclusion of RET-fusion mutation testing in the company base-case. Although routine genomic testing in advanced NSCLC may be imminent in the NHS, at current there would still be a cost involved with identifying a RET fusion-positive patient. Also, the ERG is unclear what the company exactly means with the proportion of test costs due to pralsetinib, which was arbitrarily set at 10%.
- A small error in the model for pre-treated cisplatin. In Section 4.2.4 (interventions and comparators) of the CS, the dosage for cisplatin was stated to be 75 mg for both 1st and 2nd line. In the Tables and in the model however, the actual dosage implemented for 2nd line cisplatin was 20 mg. Following the text as provided in Section 4.2.4, the ERG corrected the dosage to 75 mg for 2nd line cisplatin as well.
- It is unclear why the company marked the amount per RET fusion-positive patient attributable to pralsetinib (10%) ([redacted]) as confidential in the CS, when the £6,453 and the 10% are not?

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost effectiveness results for the untreated analysis indicated that pralsetinib is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than monotherapy pembrolizumab amounting to a ICER of [redacted] per QALY gained. In comparison to the untreated comparator of pembrolizumab plus pemetrexed plus chemotherapy, pralsetinib provides an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per QALY gained. The results of the base-case analysis in the untreated population are presented in Table 5.1.

Table 5.1: Base-case untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 73 of the CS
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years

The cost effectiveness results for the pre-treated analysis indicated that pralsetinib in comparison to docetaxel monotherapy, pralsetinib provides an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per QALY gained. In comparison to docetaxel plus nintedanib, pralsetinib provides an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per QALY gained. In comparison to platinum-based chemotherapy +/- pemetrexed, pralsetinib provides an incremental QALY gain of [redacted] at a total incremental cost of [redacted]. This represents an ICER of [redacted] per QALY gained. The results of the base-case analysis in the pre-treated population are presented in Table 5.2.

Table 5.2: Base-case pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 76 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs, quality-adjusted life years

Overall, the technology is modelled to affect QALYs by:

- Increasing PFS and OS

Overall, the technology is modelled to affect costs by:

- A higher monthly cost of treatment, compared to the majority of comparator treatments
- Its oral administration, instead of IV administration for comparator treatments
- A higher proportion of patients receiving subsequent treatment after first line, compared to comparator treatments

ERG comment: The company only provided pairwise comparisons to pralsetinib and not a fully incremental analysis as per the NICE reference case.

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 PSA with 5,000 iterations showed higher ICERs in the untreated and pre-treated analysis. The results of PSA analysis in untreated and pre-treated population are presented in Table 5.3 and 5.4 respectively.

Table 5.3: PSA untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 73 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

Table 5.4: PSA pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 76 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

The cost effectiveness acceptability curve in the untreated analysis showed that pralsetinib approximately had a [redacted] and [redacted] probability of being cost effective at willingness to pay (WTP) thresholds of £30,000 and £50,000 respectively. In the pre-treated analysis, the cost effectiveness acceptability curve showed that pralsetinib approximately had [redacted] probability of being cost effective at WTP thresholds of £30,000 and £50,000. Using a WTP of £90,000 resulted in a [redacted] probability of being cost effective, which is higher than other comparators. The cost effectiveness acceptability curve of the untreated analysis and pre-treated analysis are presented in Figures 5.1 and 5.2 respectively.

Figure 5.1: Untreated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

[redacted]

PAS = patient access scheme; QALYs = quality-adjusted life years
Source: Figure 62 of the CS[1]

Figure 5.2: Pre-treated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS = patient access scheme; QALYs = quality-adjusted life years
Source: Figure 66 of the CS[1]

[redacted]

The DSA was performed to investigate key drivers of the base-case results. Each input parameter was varied to its respective upper or lower bound and the deterministic results for the model recorded. The base-case parameter values were varied across their 95% CI where possible. In the absence of 95% CIs, parameters were arbitrarily varied +/-20%. Tornado plots show the six parameters with the largest impact on ICER. The DSA in the untreated analysis highlighted that the hazard ratios on OS and TTD had the greatest impact on the cost effectiveness results. In the pre-treated analysis the DSA highlighted that the hazard ratio for OS and the PD health state utility had the greatest impact on the cost effectiveness results.

Scenario analysis was conducted to assess uncertainty around structural assumptions of the model. The list of scenarios explored in the untreated and pre-treated analyses and their impact on cost effectiveness results are displayed in Table 5.5. The results showed that the three most influential scenarios that increased the ICER were pre-treated health state utility values, naïve comparison and discount rate 0%. The three most influential scenarios that decreased the ICER were time horizon 5, 10 and Flatiron metastases hazard ratios.

Table 5.5: Untreated and pre-treated scenario analysis

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY)		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Base-case	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25-years	5-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – costs and QALYs	3.50%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Half cycle correction	Enabled	Disabled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated OS curve selection for pralsetinib	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated OS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY)		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Pre-treated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and hazard ratios for OS, PFS, TTD	As per Flatiron analysis base-case (adjusted IPTW)	As per Flatiron analysis adjusted using matching as per Flatiron technical report	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and hazard ratios for OS, PFS, TTD	As per Flatiron analysis base-case (assuming no adjustment for metastases)	As per Flatiron analysis assuming adjustment for metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and hazard ratios for OS, PFS, TTD	As per Flatiron analysis base-case (assuming only ECOG PS 0-1 in eligibility)	As per Flatiron analysis (no ECOG PS restrictions in eligibility criteria)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and hazard ratios for OS, PFS, TTD	As per Flatiron analysis base-case	As per naïve comparison (Section B.2.9.4) of CS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib hazard ratios for OS, PFS, TTD	Assumed equal to docetaxel mono	As per naïve comparison	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method for modelling treatment duration	TTD as per ARROW	Assumed equal to PFS as per ARROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule for pembrolizumab	2-year stopping rule	No stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY)		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Proportion of patients in PBC +/- pemetrexed arm receiving pemetrexed	62.8% as per UK clinical practice	100% as per clinical efficacy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***RET* fusion testing costs**	Not included	Included as per Section B.3.5.5 of CS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated health state utility values	PF: 0.794 PD: 0.678	PF: 0.784 PD: 0.725	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.794 PD: 0.678	PF: 0.780 PD: 0.660	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated health state utility values	PF: 0.713 PD: 0.628	PF: 0.853 PD: 0.659	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.713 PD: 0.628	PF: 0.672 PD: 0.653	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 84 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; OS = overall survival; PD = progressed disease; PFS = progression-free survival; QALY = quality-adjusted life year; RET = rearranged during transfection; TTD = time to treatment discontinuation

ERG comment: The main concerns of the ERG relate to the substantial difference between deterministic and probabilistic ICER in mainly first line (for pembrolizumab monotherapy for instance, the ICER increased by 14% in PSA compared to deterministic analysis). In the clarification phase, the ERG questioned this matter and the company responded they agreed that the difference was substantial, but they had not been able to identify what the source was. The ERG has tried to find the source of the difference but was not able to detect it either. Given that it is unclear what causes the difference, the results of the PSA should be interpreted with caution.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company stated that to ensure clinical plausibility of the economic modelling, expert opinion was used for selection of appropriate distributions for survival extrapolations, and also to validate outputs from the indirect treatment comparisons.

5.3.2 Technical verification

Internal quality control and validation of the model was conducted by an external consultancy, doing cell by cell validation including formula checking and cell references. A number of pressure tests using mostly extreme values were performed.

5.3.3 Comparisons with other technology appraisals

In Table 36 of the CS, a comparison of the model features of the current appraisal with ID3743[40] was presented. Methods for the current appraisal seemed to be largely aligned with methods in ID3743. No comparison in terms of model outcomes was possible though because of in confidence information.

ERG comment: The ERG considers the validation as described by the company to be minimal and focused on mostly the use of expert opinion. As discussed in Section 4.2.2, model validation by means of an alternative model structure to the PSW (such as a state transition model) was not possible.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

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:[55]

- 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 ERG 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 ERG report, the ERG 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 ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):[56]

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

6.1.1 ERG base-case

Adjustments made by the ERG, to derive the ERG 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 ERG base-case. The 'fixing error' adjustments were combined, and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

Fixing errors

1. Key issue 6 (Section 4.2.2)
   The ERG adjusted the model to ensure that OS could not fall below PFS or TTD in the probabilistic sensitivity analysis.
2. Inconsistency in dosage of cisplatin in second line (Section 4.2.9)
   The ERG adjusted the dosing in the economic model to match the description of intervention technology and comparators in Section B.3.2.3 of the CS.

Fixing violations

3. Key issue 7 (Section 4.2.2)

The ERG adjusted the model to save additional information in PSA simulations tab enable tracking of potential violations in curves crossing. This in itself does not have any consequences for model results.

Matters of judgement

4. Issue 8 (Section 4.2.6)
   The ERG implemented treatment waning in the economic model, assuming treatment waning starting at 2 years, decreasing to a hazard ratio of one over a period of 3 years.

6.1.2 ERG exploratory scenario analyses

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

Exploratory scenario analyses

1. Issue 8 (Section 4.2.6)
   A more extreme version of the ERG preferred assumption at number 4. Assuming treatment waning starting at 1 year, decreasing over a period of 2 years
2. Issue 9 (Section 4.2.6)
   Adjusted hazard ratios, calibrated to expert opinion estimates at 3-year landmark, for OS and PFS
3. Assuming treatment duration equal to PFS (TTD = PFS for all treatment curves except per-defined treatment cut-off) because of uncertainty in TTD KM data (Section 4.2.6)
4. Assuming relative dose intensity of 90% for all treatments to test robustness of model results to potential dose reductions in clinical practice (Section 4.2.9)

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

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 ERG base-case[b]	Required additional evidence or analyses
Issue 7 - no correction for crossing curves in PSA. Overall survival could therefore fall below PFS in individual simulations of the PSA, leading to negative post progression survival.	4.2.2	Methods	Correct for crossing curves	+/- (only probabilistic ICER affected)	Yes	No
Issue 8 - constant benefit of pralsetinib assumed without justification and based on immature data	4.2.6	Unavailability – immature data	Implement plausible assumptions for treatment waning	+	Explored in ERG base-case and scenario	Yes
Issue 9 - substantial uncertainty in survival curve extrapolations due to immaturity of data	4.2.6	Unavailability – immature data	Derive hazard ratios in alternative ways	+	Explored in ERG scenario	Yes
Issue 10 - adverse event incidences included in the model potentially subject to error	4.2.7	Transparency	More precise source information needed	+/-	No	Yes
Issue 11 - lack of direct evidence to inform HRQoL	4.2.8	Unavailability of comparative HRQoL data	None – in absence of suitable data	+/-	No	Yes

[a] Likely conservative assumption (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b]Explored
ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; PFS = progression free survival; PSA = patient access scheme

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

In Section 6.1 the ERG 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 ERG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the "ERG" sheet provides an overview of the cells that were altered for each adjustment). Table 6.4 provides an overview of the fully incremental analysis the ERG performed for both the deterministic company base-case and the ERG base-case.

Table 6.2: Deterministic and probabilistic ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic CS base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic CS base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Fixing errors: Correction for crossing curves in PSA (probabilistic ICERs)					
Untreated population					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Fixing errors: Cisplatin dosage in the 2L is changed to 75 mg (effect only Platinum-based chemotherapy 2L)					
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Matter of judgement: Treatment waning OS, assuming start waning at 2 years over a period of 3 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PSA = patient access scheme; QALYs = quality-adjusted life years					

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

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 1: Treatment waning OS, assuming time till wanning 1 years over 2 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 2: Calibrated hazard ratios for comparators at 3 years for OS and PFS untreated and pre-treated populations					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 3: TTD = PFS (for all TTD curves (except treatment cut-off))					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 4: Relative dose intensity = 90% for all treatments					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALYs = quality-adjusted life years; TTD = time to treatment discontinuation

Table 6.4: Fully incremental deterministic CS and ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Deterministic CS base-case					
Untreated population					
Pembrolizumab	[redacted]	[redacted]			
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Docetaxel	[redacted]	[redacted]			
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pralsetinib 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic ERG base-case					
Untreated population					
Pembrolizumab	[redacted]	[redacted]			
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Docetaxel	[redacted]	[redacted]			
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years

Figure 6.1: Untreated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

Figure 6.2: Untreated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

6.3 ERG's preferred assumptions

For the untreated population, the estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 5.1, was [redacted] per QALY gained for pralsetinib compared to pembrolizumab monotherapy, and [redacted] per QALY gained for pralsetinib compared to pembrolizumab plus pemetrexed plus chemotherapy. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities for pralsetinib of [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY gained. For the pre-treated population, the estimated ERG base-case ICERs (probabilistic) were [redacted], [redacted], and [redacted] per QALY gained for pralsetinib compared to docetaxel, docetaxel plus nintedanib, and platinum-based chemotherapy, respectively. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities for pralsetinib of [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY gained. In both populations, the most influential adjustment was the incorporation of a treatment waning effect. The ICER increased most in the scenario analysis where alternative hazard ratios were used that were calibrated based on expert opinion of plausible OS and PFS. The fully incremental analyses demonstrated that the relevant comparators in the both the company and ERG base-case were pembrolizumab in the first line and docetaxel in the second line.

6.4 Conclusions of the cost effectiveness section

A comprehensive selection of databases and resources were searched, and the searches were transparent and reproducible. The same SLR searches performed to identify clinical effectiveness evidence were used to identify cost effectiveness studies, HRQoL studies and costs and healthcare resource use studies. Overall, the ERG does not have any major concerns regarding the searches.

The eligibility criteria used by the company provided sufficient detail and were suitable to fulfil the company's objective to identify cost effectiveness studies.

The CS was largely in line with the NICE reference case. The CS partly deviated from the scope however, where it concerned the comparators modelled. More specifically, atezolizumab in the 2nd line was excluded as a comparator, while expert opinion indicated that it is a relevant treatment option. Also,

the company did not perform a fully incremental analysis but only provided pairwise comparisons to pralsetinib.

Although the ERG agreed that a partitioned survival model seemed appropriate for the decision problem, they would have liked to see a state transition model as a scenario to validate the results of the company's partitioned survival model.

The ERG considered the absence of any waning of the treatment effect in the company model not well justified. Data from the ARROW trial are not sufficiently mature to assume a continuous effect of pralsetinib. Given the median follow-up in ARROW of around 13 months overall and 9.5 months for the untreated population (which was the main focus of this appraisal according to the company) the ERG believes that implementing a gradual waning of the treatment effect over 3 years, starting from the 2-year point, is a fair assumption.

A major concern of the ERG was the curve selection for extrapolating OS, PFS and TTD and the hazard ratios applied to derive the comparator curves. The selection seemed to be largely driven by clinical expert opinion, with the final choice of distribution often being in favour of pralsetinib relative to the comparators. The ERG believes that altogether, the way effectiveness was modelled by the company is subject to substantial uncertainty, beyond what the ERG was able to take into account in their ERG base-case analysis.

With respect to AEs in the economic model, there was a lack of clarity on where the incidence rates came from. For many of the incidences used, the ERG could not reproduce the rates with the sources provided. Also, for pralsetinib there were inconsistencies in AE rates between the clinical study report and the CS. On the whole however, the ERG considers these potential errors to be of minor importance to the overall cost effectiveness results.

With respect to the implementation of health state utility values in the model, the ERG had some concerns which mostly had to do with the absence of direct evidence on HRQoL for this appraisal. The company chose to inform the model using health state utility values from previous appraisals, but these were not specific for RET fusion-positive patients. Also, in the company base-case, different sources were used to inform untreated and pre-treated populations. This led to a substantial difference in utility scores between the two populations, although in the mapped EORTC-QLQ C30 data the company provided at clarification, there was no difference observed between populations. This made the ERG question the suitability of the utility values applied in the model. It is difficult to say however what would have been the correct approach in the absence of valid comparative data from a RET fusion-positive population.

The ERG also questioned the assumption of equal health state costs for the untreated and pre-treated populations, given that everything else in the model was split out by population, under the rather explicit assumption that the pre-treated population was less healthy, even when progression free (hence the difference in utility values).

The ERG made various adjustments to the company base-case and presented a fully incremental analysis for the company base-case and the ERG base-case. In the untreated population (first line) the probabilistic ERG base-case ICER for pralsetinib versus pembrolizumab monotherapy was [redacted] per QALY gained (based on 10,000 iterations). For pralsetinib versus pembrolizumab plus pemetrexed plus chemotherapy, the ICER was [redacted]. The most influential scenario was the analysis using alternative hazard ratios calibrated based on expert opinion, driving the ICER substantially upwards.

In the pre-treated population (second line), the probabilistic ERG base-case ICER for pralsetinib versus docetaxel was [redacted] per QALY gained (based on 10,000 iterations). For pralsetinib versus docetaxel plus nintedanib the ICER was [redacted] per QALY gained, and for pralsetinib versus platinum-based chemotherapy, the ICER was [redacted] per QALY gained. The most influential scenario was the analysis using alternative hazard ratios calibrated based on expert opinion, driving the ICER upwards.

In conclusion, cost effectiveness estimates of pralsetinib in the first line are subject to considerable uncertainty, mainly because of immaturity of data, small sample size, and lack of comparative evidence in various areas. The ERG considers the clinical evidence presented to be not sufficiently robust to inform the economic model. Even when all the ERG preferred assumptions were implemented in the model, uncertainty remained on a number of issues, such as the appropriateness of the hazard ratios and the methods and data used to derive them, long-term efficacy of pralsetinib, and comparative HRQoL values. In the second line these uncertainties are present as well, but the ICERs for the second line comparisons are well outside the cost-effective range, and therefore the uncertainty has less of an impact on decision making.

7 END OF LIFE

According to the CS, pralsetinib in its full anticipated licensed indication does meet the NICE criteria for an end of life medicine, see Table 7.1.[1]

Table 7.1: End of life criteria

Criterion	Data available	Reference in CS (Section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	There is a paucity of outcome data for *RET* fusion-positive NSCLC patients in the second line setting and beyond; however, historical outcomes seen with second line chemotherapy regimens in patients without targetable molecular drivers are poor, with ORR ranging from 3.3% to 9.1%, median PFS not exceeding 3.4 months and median OS ranging from 7.9 to 10.9 months. [1]	B.1.3.1.2, pages 28-30
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	"Mean OS in the economic model for untreated pralsetinib is estimated to be 57.8 months. Therefore, it's estimated that pralsetinib leads to an extension to life of 35.3 months and 37.1 months against untreated pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy respectively. Mean OS in the economic model for pre-treated pralsetinib is estimated to be 46.0 months. Therefore, it's estimated that pralsetinib leads to an extension to life of 30.5-32.8 months against pre-treated comparators. Clinical experts confirmed to Roche that treatment with pralsetinib would extend life by greater than 3 months."	B.2.6.2, page 59

Based on Table 20 of the CS[1]
CS = company submission; CI = confidence interval; KM = Kaplan-Meier; MAIC = matching adjusted indirect comparison; NSCLC = non-small cell lung cancer NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RET = rearranged during transfection

ERG comment:

- The ERG considers the first criterion, life expectancy less than 24 months, to be met.
- Regarding the second criterion, extension of life of ≥3 months, the ERG can confirm from the results of the economic analysis that the gain in LYs was calculated to be over 2 years versus all comparators:
    - In the untreated population, Pembrolizumab + pemetrexed + chemotherapy or Pembrolizumab monotherapy
    - In the pret-reated population, Docetaxel monotherapy, Docetaxel + nintedanib and Platinum-based chemotherapy +/- pemetrexed
- However, the ERG has concerns regarding the validity of the evidence referred to by the company, see Key issues 4 and 5. Moreover, to demonstrate that the second criterion is met, robust

comparative data must be provided whereas no formal comparison was performed for some comparisons (see Key issue 2).

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer [ID3875]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 28 October 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect labelling selpercatinib manufacturer

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 2.1, page 31 "*and [the company responsible for selpercatinib] Roche*"	Roche are not responsible for selpercatinib. The sentence should read: "*and [the company responsible for selpercatinib] Eli Lilly"*	Typographical error	Corrected.

Issue 2 Incorrect labelling of pembrolizumab monotherapy subsequent treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.9.5, Table 4.18, page 101 Pembrolizumab monotherapy costs reported as 4,789	Pembrolizumab monotherapy costs are 3,789 as per Section B.3.5.4.3, table 69, page 166 of the company submission	Typographical error	Corrected.

Issue 3 Incorrect labelling of issue numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 6.1.3, table 6.1, page 111 Issues are numbered 6-10. However the description of the issues relates to issues 7-11	Update issue numbers to 7-11	Typographical error	Issue numbers updated in table 6.1 (page 111) and also in sections 6.1.1 and 6.1.2 on page 110

Issue 4 Incorrect representation of company submission reporting of the eligibility for end-of-life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 7, page 122 "*According to the CS, pralsetinib in its full anticipated licensed indication as a second- or subsequent line therapy does not meet the NICE criteria for an end of life medicine*"	The company submission states (Section B.3.11.4, page 200): "*Pralsetinib meets the NICE end-of-life criteria in both the untreated and pre-treated setting*" This is evidenced by the information provided in Section B.2.13, Table 34, page 108-9. It is unclear why the ERG has chosen only to report the second- or subsequent line of therapy and exclude the untreated population in this sentence. Therefore, the sentence should read: "*According to the CS, pralsetinib in its full anticipated licensed indication does meet the NICE criteria for an end of life medicine*" If it is the ERG's view that pralsetinib does not meet the end-of-life criteria this should be stated in the 'ERG comments' section and not reported at the start of the section as if it is the view of company submission as this is not the case.	This statement is an inaccurate representation of the company submission.	Section 7 has been amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Section 3.4, page 64	"pembrolizumab plus chemotherapy (n=5), platinum-based chemotherapy (n=1), immunotherapy monotherapy (n=1) and other (n=3). In the untreated analysis, results favoured pralsetinib over best available therapy (OS HR 0.40, 95% CI 0.14, 1.16; PFS HR 0.67, 95% CI 0.30, 1.48; TTD HR 0.68, 95% CI 0.32, 1.44)."	pembrolizumab plus chemotherapy ([redacted]), platinum-based chemotherapy ([redacted]), immunotherapy monotherapy ([redacted]) and other ([redacted]). In the untreated analysis, results favoured pralsetinib over best available therapy ([redacted]).	Corrected.

(Please add further lines to the table as necessary)

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Technical engagement response form

Pralsetinib for RET fusion-positive advanced non-small cell lung cancer [ID3875]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

Technical engagement response form

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 6 December**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roche Products Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	--

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1. The appraisal population is restricted to those with non-squamous NSCLC cell lung cancer which limits generalisability to patients with squamous NSCLC	No	The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced non-small cell lung cancer (NSCLC). The company acknowledges that the population of rearranged during transfection (*RET)* fusion- positive squamous NSCLC patients is rare. The small proportion of squamous *RET* fusion-positive NSCLC patients enrolled in ARROW (1.4%) is expected to be reflective of what would be observed in United Kingdom (UK) clinical practice. European Medicines Agency (EMA) regulatory authorities considered that results were generalisable enough from non-squamous to squamous patients to grant a licence in the squamous indication. Due to the unmet medical need in all *RET* fusion-positive patients in the UK, it is crucial that all *RET* fusion-positive advanced NSCLC patients (non-squamous and squamous histologies) have a *RET* inhibitor available as a treatment option in line with the proposed licensed indication. The selpercatinib appraisal consultation document (ID3743, Section 3.5, page 8) states that the company clinical expert expected there to be some level of response in squamous patients.(1) In addition it is also mentioned that the Cancer Drugs Fund (CDF) clinical lead said that the National Health Service (NHS) would follow the same recommendation in treatment for squamous NSCLC as for patients with non-squamous NSCLC and therefore, the committee agreed that the technology appraisal would apply to both squamous and non-squamous advanced NSCLC. Given the similar nature of the

<table>
<tr><td></td><td></td><td>squamous issues across the two appraisals, the precedent set by ID3743 is adequate to cover the appraisal for pralsetinib and that the relevant population for this appraisal should be the full licenced indication including squamous patients.</td></tr>
<tr><td>Key issue 2. Exclusion of potentially relevant comparators listed in the NICE scope</td><td>No</td><td>Treatment comparators for this appraisal should reflect the current standard of care for RET fusion-positive patients in the NICE treatment pathway.

<u>Untreated: Chemotherapy in combination with a platinum drug +/- pemetrexed treatment</u>

Roche acknowledges that both the clinical expert in the Evidence Review Group (ERG) report and the response from British Thoracic Oncology Group (BTOG) suggest that chemotherapy in combination with a platinum-based chemotherapy +/- pemetrexed treatment should be included as a comparator. We note the BTOG response states that patients “would follow NICE guidelines” (Section 9, page 4 (296)). We agree that for wild-type (WT) advanced NSCLC, chemotherapy in combination with a platinum-based chemotherapy +/- pemetrexed treatment would represent standard of care.

However, it is key that the comparator population in this appraisal are patients with (detected or undetected) RET fusion-positive advanced NSCLC. In a retrospective analysis examining the characteristics of patients with RET fusion-positive NSCLC in real-world practice in the United States, 46 patients were identified as RET fusion-positive out of a sample size of 5807.(2) Table 3 below provides an illustration of the clinical characteristics of RET+ and RET- cohorts. These patients demonstrate differing characteristics to WT NSCLC patients. RET fusion-positive patients tend to be younger, have never smoked and are more likely to have Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0-1 compared to WT NSCLC patients. These characteristics can be considered key differentiators in choice of treatment.

Table 3: Clinical characteristics of RET+ and RET- cohorts
<table>
<tr><th>Characteristics</th><th>RET+ (n=46)</th><th>RET - (n=5761)</th><th>RET+ vs RET- P value*</th></tr>
<tr><td>Age, years (mean, Sd)</td><td>62.9 (11.0)</td><td>67.2 (10.2)</td><td>0.004</td></tr>
<tr><td>Stage IV at initial</td><td>34 (73.9)</td><td>3680 (65.2)</td><td>n/a</td></tr>
</table></td></tr>
</table>

diagnosis, n (%)				
Histology, n (%) non-squamous squamous missing/unknown	 45 (100.0) 0 (0.0) 1	 4392 (79.4) 1138 (20.6) 231	<0.0001
Smoking history smoking history no smoking history	 17 (37.0) 29 (63.0)	 4703 (81.9) 1042 (18.1)	<0.0001
ECOG performance score, n (%) 0 1 2 3+ missing/unknown	 19 (61.3) 9 (29.0) 2 (6.5) 1 (3.2) 15	 1419 (33.6) 2079 (49.2) 593 (14.0) 135 (3.2) 1535	0.02

Platinum-based chemotherapy was not included as a comparator based on the following evidence:

- Roche conducted an advisory board with six leading UK NSCLC clinical experts in order to determine standard of care for *RET* fusion-positive patients. Clinical experts were asked what was considered standard of care for *RET* fusion positive patients or WT patients who demonstrated representative characteristics of *RET* fusion patients. Clinical experts stated that ECOG PS was a key determinant in the treatment decision. Patients with higher ECOG PS were more likely to receive platinum-based chemotherapy regimens. Therefore, given the better ECOG PS status among *RET* fusion positive patients, it was recommended platinum-based chemotherapy regimens should not be considered standard of care.
- Similar feedback was received in a recent qualitative questionnaire with clinicians in lung cancer which indicated that a key motivation for prescribing chemotherapy regimens in the first-line setting is that this is for patients who are not able to tolerate pembrolizumab + pemetrexed + chemotherapy (i.e. worse ECOG PS patients).(3)

		● The appraisal company clinical expert has also commented that there is not a lot of use of platinum doublet chemotherapy in the *RET* fusion-positive first line untreated setting and therefore, advised the company to exclude this as a potentially relevant comparator in the untreated population. ● In the selpercatinib appraisal consultation document (TA10618, Section 3.2, page 5-6) the committee agreed that nearly all patients receive immunotherapy +/- chemotherapy combination in the first line setting, suggesting that pembrolizumab + pemetrexed + chemotherapy is the true standard of care for *RET* fusion-positive patients and any use of chemotherapy treatment alone would be negligible.(1) The committee therefore concluded that immunotherapy treatment should be removed as comparators from the second-line setting. *Untreated: other comparators excluded* The ERG report (Section 2.3) also states, based on clinical expert opinion that the following comparators are also missing: nivolumab plus ipilimumab, atezolizumab monotherapy and atezolizumab plus bevacizumab plus carboplatin plus paclitaxel. Roche notes that these comparators all have licensed indications in this setting. However, comparators in the submission should represent the standard of care in a setting. The company submission (Table 1 and 2, page 13-16) outlines the non-squamous untreated and pre-treated comparators suggested by National Institute for Health and Care Excellence (NICE) in the final scope, with justification for their inclusion or exclusion. For these three treatments stated above, further justification is given below: ● Nivolumab with ipilimumab and chemotherapy (TA724) has not been recommended by NICE for use within its marketing authorisation ● In the professional submission by BTOG they did not advise that any of the above comparators should be considered standard of care the above comparators as first line treatments of choice. (BTOG Professional organisation submission, page 4-5) ● The appraisal company clinical expert mentioned that there is minimal usage of atezolizumab, bevacizumab, carboplatin plus paclitaxel in the relevant appraisal population

		Untreated: comparators included As per advice received in the advisory board, from the company clinical expert and following advice from the committee in the selpercatinib appraisal, the untreated comparators in the updated company base case have remained unchanged: ● Pembrolizumab + pemetrexed + chemotherapy ● Pembrolizumab monotherapy. *Pre-treated comparators* The following comparators from the NICE scope have been excluded from the comparator list in this submission: ● Selpercatinib: ○ As stated in the selpercatinib company submission, the submission sought access via the CDF. Selpercatinib is now listed in the CDF for the pre-treated setting (2nd line) and is therefore not eligible to be a comparator in this setting. ● Atezolizumab monotherapy/ atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP)/ pembrolizumab monotherapy: ○ Patients are not eligible for any immunotherapy re-challenge regardless of line of therapy. As mentioned in the untreated comparators sections patients are expected to receive immunotherapy (combination or monotherapy) in the untreated setting and therefore, any immunotherapy agent in the second line setting is not considered to be an eligible comparator. This is an identical approach to that taken and approved by the committee in the selpercatinib appraisal consultation document (Selpercatinib ACD, section 3.2, Page 6). The committee concluded that docetaxel and docetaxel with

		nintedanib were the appropriate comparators for pre-treated patients with *RET* fusion-positive NSCLC. Therefore, as per advice received in the advisory board, from the company clinical expert and following advice from the committee in the selpercatinib appraisal (ID3743), the untreated comparators in the updated company base case have remained unchanged: ● Docetaxel monotherapy ● Docetaxel + nintedanib ● Platinum-based chemotherapy +/- pemetrexed maintenance (in PD-L1 ≥50%) (which represents a combination of platinum doublet and pemetrexed with carboplatin, as per clinical expert advice from the advisory board) *Squamous* There was a very small number (1.3%, 2/233, total efficacy population) of squamous patients enrolled into the ARROW study and therefore a squamous subgroup analysis/indirect treatment comparison is not considered feasible. As per the ERG report (page 31), there is mention that a NICE clinical expert noted the following: *"the company is making the assumption that RET fusions are so rare in S NSCLC that only the NS NSCLC pathway needs to be considered. From the TA point of view I think this is reasonable as it makes things simpler (NHSE will allow use of pralsetinib in patients with RET fusion S NSCLC in any case if the current indication is recommended)".* *Best supportive care (BSC)* Given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate, or are willing to have pharmacological intervention will be eligible for pralsetinib, hence, BSC is not an appropriate comparator for this appraisal.

<table>
<tr><td></td><td></td><td>The selpercatinib ERG report (Section 2.5, Table 4, page 29) also recommended the exclusion of BSC as a comparator.</td></tr>
<tr><td>Key issue 3. Questionable generalisability to UK population</td><td>No</td><td>ARROW is a Phase 1/2, multicentre, non-randomised, open-label, multi-cohort study, with the Phase 2 dose expansion phase conducted in 13 countries. UK clinical experts confirmed to Roche that the enrolled population is similar to other oncogenic driver clinical trials which have been used as evidence sources for UK health technology appraisal (HTA). (4, 5) Therefore, the study population can be considered generalisable to UK clinical practice and applicable for decision making.

Table 4 below shows a side by side comparison of the baseline demographics for RET fusion positive NSCLC patients for both ARROW and LIBRETTO-001 studies. Both data sets are closely matched demonstrating that a typical RET fusion-positive patient is younger than an average WT NSCLC patient and they have better performance scores and tend to be non-smokers.

Table 4: Comparison of pralsetinib and selpercatinib baseline characteristics
<table>
<tr><th>Characteristics</th><th>Pralsetinib (ARROW) Measurable Disease Population n=216 (Company Submission, Table 8, page 43)</th><th>Selpercatinib (LIBRETTO-001) Total population n=253 (Company Submission, Table 9, page 52)</th></tr>
<tr><td>Median age, years (range)</td><td>60.0 (26-87)</td><td>61.0 (23-86)</td></tr>
<tr><td colspan="3">Race, %</td></tr>
<tr><td>White</td><td>52.3</td><td>51.4</td></tr>
<tr><td>Asian</td><td>38.4</td><td>40.7</td></tr>
<tr><td>Other</td><td>0.9</td><td>3.2</td></tr>
<tr><td colspan="3">ECOG performance status, %</td></tr>
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<table>
<tr><td>0</td><td>33.8</td><td>36.8</td></tr>
<tr><td>1</td><td>63.4</td><td>61.3</td></tr>
<tr><td>2</td><td>2.8</td><td>2.0</td></tr>
<tr><td colspan="3">Smoking history, %</td></tr>
<tr><td>Never</td><td>61.6</td><td>69.6</td></tr>
<tr><td>Former</td><td>34.3</td><td>28.5</td></tr>
<tr><td>Current</td><td>2.8</td><td>2.0</td></tr>
<tr><td>Missing/Unknown</td><td>1.4</td><td>0</td></tr>
</table>

The company also highlight the professional organisation submission provided by BTOG (Section 18, page 11), who stated the following when asked whether the clinical trial on the technology reflect current UK clinical practice:

“Yes, beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice”.
</td>
</tr>
<tr>
<td>Key issue 4. Methodological problems with systematic literature reviews</td>
<td>No</td>
<td>The Systematic Literature Reviews (SLRs) submitted were performed in accordance with NICE guidelines and supported methods, and reported according to PRISMA guidelines.(6-9) Limitations associated with evidence generated were acknowledged in the submission but they are related with the lack of evidence available in the population under assessment and not with the methodologies used. All efforts were made to overcome the limitations identified. Despite the methodological issues pointed out by the ERG, with which the company disagrees, there is no evidence that relevant studies/evidence were missed. It should be noted the ERG has not presented additional suggestions.

<u>RET-fusion positive NSCLC SLR (SLR 1)</u></td>
</tr>
</table>

		• Search: The ERG note that trials registers were not searched and that the search facet for *RET* might have benefited from the inclusion of more synonyms (ERG report, Section 3.1.1, page 36-7). The search approach conducted took into consideration all core databases identified in NICE guideline, including Cochrane Central Register of Controlled Trials (CENTRAL).(6, 7) Regarding the search terms used to build the strategy, as mentioned in NICE guidelines, although it is important that searches for systematic reviews attempt to identify all the relevant literature, there needs to be a trade-off between sensitivity and precision, in a way to not compromise the feasibility of the study. The most important point is to run quality checks in the search develop to ensure that relevant trials were not missed.(6-8) Although Roche acknowledge that further terms could have been used to describe *RET* population, efforts were made to check the quality and accuracy of the search strategy used, namely the verification of search strategies against literature available; run searches with and without certain search terms and assess the differences between the results obtained; check the bibliographies of included studies to ensure that all relevant papers have been retrieved by the search strategy used. For all mentioned, Roche believe that the searches conducted were explicitly and transparently shared and follow the guidelines and best practice. The search strategy does not compromise any conclusion that might come from the assessment of the SLR results and therefore should not be viewed as a barrier to access. Furthermore there is no evidence that important evidence has been missed. • Eligibility criteria: The ERG note eligible comparators for SLR 1 are not clear from the study eligibility information presented. Therefore, the nature of the treatment comparisons at this stage of the evidence synthesis is uncertain and it is unclear to what extent the selection of comparators reflects current practice in the UK NHS (ERG report, Section 3.1.2, page 41) The objective of the SLR was to assess the clinical evidence available for the treatment of patients with locally advanced or metastatic *RET*-fusion positive NSCLC and to allow a comparison of pralsetinib with relevant comparators used in clinical practice. Considering the expected challenges in finding

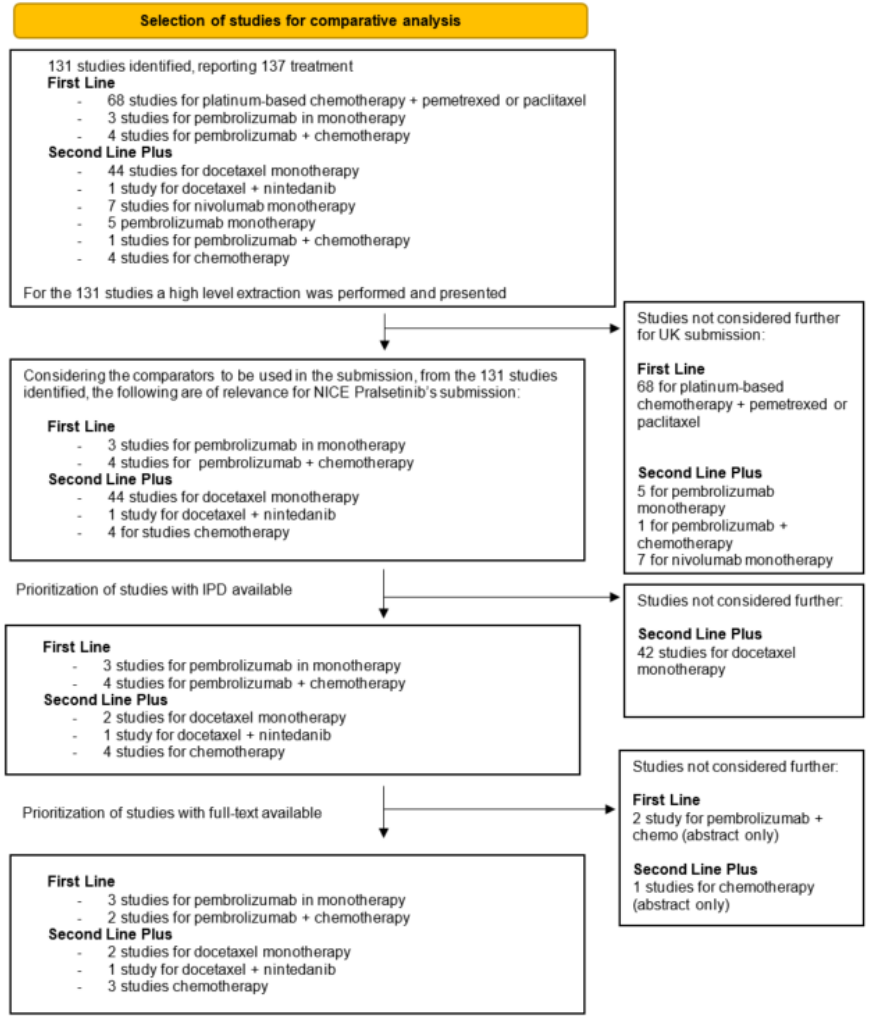
		evidence in this population, no restrictions were defined for the intervention/comparators in the eligibility criteria. This allowed any study in the *RET*-fusion positive population to be considered for assessment regardless of the intervention used. The ERG states that "*it is unclear to what extent the selection of comparators reflects current practice in the UK NHS*". Once there was no restriction in the eligibility criteria, the interventions used in the current practice in the UK NHS are naturally included in the list and there is no risk in missing important information regarding those interventions due to the eligibility criteria defined. • Data Extraction: The ERG state the data extraction process for SLR 1 is not in line with recommended good practice i.e., dual, independent data extraction, particularly for outcome data. The ERG does not consider that the process described by the company would sufficiently address the risk of bias or error (ERG report, Section 3.1.3.2, page 44) According to the SLR methods supported by NICE (2), "*The number of researchers that will perform data extraction is likely to be influenced by constraints on time and resources, (...) as a minimum, one researcher should extract the data with a second researcher independently checking the data extraction forms for accuracy and detail. If disagreements occur between assessors, they should be resolved according to a predefined strategy using consensus and arbitration as appropriate*." During the clarification questions phase, Roche shared in detail the process for data extraction in this review, that consisted of having one reviewer doing the initial extraction and a second reviewer confirming the extraction performed by: o Reviewing the publication(s) associated with the study for extraction, highlighting any relevant data for extraction o Checking that all data from the publication(s) had indeed been extracted into the DET in the correct cell (in this way, any data 'missed' by the first extractor was included in the Excel sheet – any additional data extracted were highlighted and checked by the first extractor [any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser])

		○ Checking that the correct values had been extracted (any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser) Roche believe the process followed was compliant with NICE guidelines and should therefore not be the reason to question the robustness of the results presented. • Quality Assessment: The ERG state the rationale for excluding some studies from the methodological assessment table (Table 10) was not explained (ERG report, Section 3.1.4.1, page 45) The main goal of the SLR was to identify the clinical evidence to support the indirect treatment comparisons of pralsetinib versus standard of case, and ultimately inform the cost-effectiveness analysis. Therefore, a feasibility assessment (FA) was conducted to identify which of the studies included in the SLR could be further assessed and be used to generate comparative evidence. For that reason, although 38 studies were included in the SLR only 8 were included in the indirect treatment comparisons (ITCs). The quality assessment is presented for the studies that passed the FA and were included in the ITCs, as this is the information used to inform the cost-effectiveness analysis. All the studies that were included in the SLR but excluded at the FA step were not extracted or assessed further and have no impact in the submission. *WT NSCLC SLR (SLR 2)* Considering the significant data gaps resulting from SLR 1, a complementary method was explored considering not only patients with *RET* fusion-positive NSCLC, but also WT patients. For that, a new and independent SLR with a new research question was designed and conducted. It is important to note that with this not being the main clinical SLR in the submission and considering the amount of evidence available for NSCLC WT in any treatment line, some prioritization exercises were needed to ensure the feasibility of the analysis without compromising the quality of results obtained. Additionally, once different research questions and objectives were defined for the two SLRs, it is not inadequate

		that different methodologies (searches, eligibility criteria etc.) were used as well, especially considering that those (question and goal of a review) are the main drivers for the methodology definition. • Search Unlike the scenario of the first review in *RET*-fusion positive population, in the WT space there is a huge amount of data available, especially when considering all lines of treatment. As described in the SLR methods supported by NICE,(8) scoping searches may provide a good understanding of the evidence available for a certain scope, and researchers have the option of justifying a decision to limit study design based on the results obtained in such preliminary assessment. While in some cases there are evidence gaps clearly identified and a range of study designs may be needed to address the research questions, in others it becomes very obvious that the scope in question is quite populated. Additionally, according to NICE guidelines, "*Depending on the review question, it may be appropriate to limit searches to particular study designs. For example, for review questions on the effectiveness of interventions, it may be more efficient to search for systematic reviews, followed by controlled trials followed by observational studies. This prevents unnecessary searching and review work*." Based on the knowledge in the space and the results of preliminary assessments showing a lot of evidence available for the WT NSCLC, and considering what is referred in the guidelines in terms of the studies designs to be considered, Roche believe that the prioritization of randomised control trials (RCTs) over other study designs does not compromises the findings of the SLR. Regarding the broadness of the search strategy used, as mentioned for SLR 1, although it is important that searches for systematic reviews attempt to identify all the relevant literature, there needs to be a trade-off between sensitivity and precision, in a way to not compromise the feasibility of the study. The most important point is to run quality checks in the search develop to ensure that relevant trials were not missed. Although Roche acknowledge that further terms could have been used to describe NSCLC, efforts were made to check the quality and accuracy of the search strategy used. • Eligibility criteria

		Considering that the goal of the SLR was to inform the cost effectiveness assessment, the outcomes used in the economic mode (PFS, OS) were used to prioritize the list of outcomes to be included. For endpoints related with safety please also consider the points raised in response to key issue 5, where it is shown that indirect comparison of safety endpoints is not feasible and the impact in the model is not significant. However, from the 14 studies excluded based on outcomes at full publication review, there were no studies that reported relevant clinical outcome data for treatment arms of interest (and so none of the studies could have been considered for inclusion in the analyses, even if further outcomes were considered in the eligibility criteria). Most of the publications excluded based on the "outcomes" were protocols or reported non-clinical/safety outcomes e.g. VEGF/MMP9 expression levels. • Study selection After running the searches and screening the records according to the eligibility criteria defined, the SLR included 131 studies to move forward for feasibility assessment. The process to select studies for comparative analysis is described in Figure 1. It is important to note that given the source of data for pralsetinib (single-arm study), limited comparative options are available. In this scenario the following option can be performed: o Propensity score analysis (adapting for important prognostic factors) when individual patient data (IPD) is available for both studies (pralsetinib and comparator) o Matching adjusted indirect comparison (MAIC) adjusting pralsetinib patients the comparator arm. This option adjusts away all population particularities of *RET*-fusion positive patients so is not considered appropriate for the intent goal o Naive comparisons where there are no population adjustments. In this case it is important that the population characteristics of the comparator's arm are as close to ARROW as possible. Considering the options available, and having in mind that no network analysis is possible, it seems appropriate to prioritize studies to which IPD is available. In addition, as results of different studies are not being connected, having more than one study per comparator does not bring additional value. For that reason one study per comparator was prioritized.

Figure 1: Selection of studies for comparative analysis



		From the final list of studies, one of the studies for chemotherapy in 2L was reported in a Chinese paper. This was assessed based on title and abstract information but it was not translated for further inclusion. The ERG stated: "*The ERG is not convinced that sample size and/or ethnicity are appropriate reasons for exclusion (ethnicity is not listed as an exclusion criterion for SLR 2) and therefore it would have been preferable to have this paper translated and include the comparator data*" (ERG report, Section 3.1.2, page 43). The following issues indicate that the translation and inclusion of this publication would not have impacted the analyses presented: o The only arm relevant from this study is pemetrexed combined with platinum (n=55) - comparative analyses with pemetrexed followed by carboplatin (GOIRC 02-2006 + NVALT7: naïve comparison) and carboplatin or cisplatin plus pemetrexed (IMpower132: PSA) are already available and are based on larger sample sizes o Thus, although sample size was not a criterion for selection into the SLR/analyses, it is important to note that the study size is notably smaller than the studies included in the SLR/analyses and selected for comparative analyses; thus this study would not have been selected for comparative analyses o The comparative analyses focussed on OS/PFS but the Wang 2017 English abstract states that only short-term clinical effects are reported (follow-up time not explicitly reported), with the results stated as differences in PFS/OS between groups with no HRs presented – therefore, it is likely that the survival data are immature and presented in the format of OS/PFS rates at 1 year with no HR available On an additional note, the citation of this article was Wang C. et al. Comparison of docetaxel and pemetrexed combined with platinum in treatment of NSCLC after failure of gefitinib therapy. [Chinese]. 2017; 32(2):164-167, whereas the article cited on p.43 of the ERG report and cited as ref 22 was Wang J, Zhang S. [Targeted therapy for advanced non-small cell lung cancer in the elderly]. Chin J Lung Cancer 2009;12(7):821-5. The final list of studies considered appropriate for comparative analysis is outlined in the Company Clarification response (B25, Table 23, page 44). Study selection using sample sizes was applied only

		for docetaxel in the pre-treated setting. In this case, considering that POPLAR is a phase II study, compared to OAK which is phase III and therefore represents a more robust evidence base to perform the comparison. About the general process of study selection for the comparative analysis, the ERG "*questioned why only PDL-1 status, histology; pooled analyses; or studies with the largest sample size were the only criteria for matching with the ARROW study*". As it is possible to understand from the points mentioned above those were not the only points considered. Because those were the differentiating points they represent the rationale for exclusion for some of the studies, but all the characteristic of the studies and eligibility criteria of the SLR were considered. The company believes that the process allowed a transparent and unbiased assessment of the evidence available and there is no evidence that important studies were missed or that other relevant data was not included. • Data extraction See corresponding section in SLR 1. • Quality assessment The assessment was conducted and is displayed in Appendix 1. However, it is important to mention that as only naive comparisons are performed with the data from those studies and only one arm of the study was considered, randomization is lost and most of the points in the quality assessment are not of relevance.
Key issue 5. Lack of comparative safety data	Yes	As per the company response to clarification question 25 (d), ITCs of safety outcomes are not feasible. There are different mechanisms of action, different treatment durations, follow-up times and trial designs which make a comparison potentially misleading. Additionally, very limited data is available for the comparators studies with most of the adverse events being grouped (e.g. any adverse event, any treatment related adverse event), which does not allow the differentiation in the safety profiles of the different treatments. This is worsened by the fact that mainly naive comparison would have been

		possible with very few safety endpoints per comparator, and not allowing for proper adjustments. In light of the above limitations of comparative safety analyses, this is not an appropriate analysis to conduct in this setting. A descriptive safety analysis of pralsetinib compared to pembrolizumab + pemetrexed + chemotherapy in the untreated setting is provided in Appendix 2. *Clinical expert opinion* We note that in the statement from BTOG, no concerns were held regarding the safety profile of pralsetinib suggesting that it is likely to be favourable in comparison to current standard of care: "*Although formal, comparative, Quality of Life data has not been published, Pralsetinib has been to have a favourable side-effect profile. In ARROW, common grade 3 or worse treatment-related adverse events were neutropenia (18%), hypertension (11%), and anaemia (24 [10%). There were no treatment-related deaths in this population. Current chemotherapy / chemoimmunotherapy combinations have a worse side effect profile than this. The combination of greater efficacy, longer duration of activity, and more favourable profile is highly likely to result in improved Qualitty* [quality] *of Life compared to standard of care, for patients receiving Pralsetinib*. […] *From the patient perspective, the drug will be easier to take (fewer side effects)*" (BTOG Professional organisation submission, page 8). *Impact on results* In terms of cost-effectiveness, the impact of comparative safety data on results is negligible. For example, in the pralsetinib untreated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. The absence of comparative safety data should represent a substantial barrier to access. We note that in the selpercatinib appraisal (which also represented a single-arm study in *RET* fusion positive advanced NSCLC), no comparative safety data was provided and this was not viewed as a key concern either by ERG or committee.

		Future evidence The issue of comparative safety will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of *RET* fusion-positive, advanced NSCLC. Recruitment is expected to be completed in [redacted] with results expected in [redacted].
Key issue 6. Propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed	Yes	*Untreated setting* As per the response to key issue 2, platinum-based chemotherapy +/- pemetrexed is not standard of care for *RET* fusion positive advanced NSCLC patients and therefore was not included as a comparator in the submission. Therefore, a comparison using the Flatiron EDM dataset is not seen as necessary. *Pre-treated setting* As part of the initial submission, Roche investigated the feasibility of using the Flatiron EDM dataset to inform the platinum-based chemotherapy +/- pemetrexed arm of this comparison. The results of this comparison were provided in the Flatiron indirect treatment comparison technical report provided as part of the submission reference pack (EDM SCA Pralsetinib vs EDM cohorts for NSCLC, Appendix G, Section 9.7.3, pages 214-233). In the Flatiron EDM dataset, 177 (pre-adjustment) patients were identified as having received platinum-based chemotherapy +/- pemetrexed as second-line treatment. Table 5 shows that age and race are highly imbalanced, and smoking history and metastases-related variables are severely imbalanced. The remaining variables are all imbalanced to some extent as well. Note however that since metastases are underreported in the EDM, related variables are not used for adjustment and residual imbalances are not considered to be a crucial factor in determining the reliability of the analysis.

Table 5: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given platinum-based chemotherapy +/- pemetrexed in pre-treated setting

	Level	Platinum-based chemotherapy	Pralsetinib	SMD
n		[redacted]	[redacted]	
Age (%)	< 65	[redacted]	[redacted]	0.627
	>= 65	[redacted]	[redacted]	
Sex (%)	F	[redacted]	[redacted]	0.205
	M	[redacted]	[redacted]	
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	1.371
	No history of smoking	[redacted]	[redacted]	
ECOG (%)	0	[redacted]	[redacted]	0.067
	1	[redacted]	[redacted]	
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.175
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.342
	STAGE IV	[redacted]	[redacted]	
Race (%)	White	[redacted]	[redacted]	0.534
	Other	[redacted]	[redacted]	
	Unknown	[redacted]	[redacted]	
Sum of total metastases (median [IQR])		[redacted]	[redacted]	2.473
Metastases (%)	Isolated brain/CNS site	[redacted]	[redacted]	3.735
	None	[redacted]	[redacted]	
	Other	[redacted]	[redacted]	
Brain/CNS metastasis only (%)	0	[redacted]	[redacted]	0.803
	1	[redacted]	[redacted]	
Liver metastasis only (%)	0	[redacted]	[redacted]	0.494
	1	[redacted]	[redacted]	

Following weighting, Table 6 shows that only time from initial diagnosis is balanced among covariates used for adjustment (SMD<0.1). The remaining variables are at least moderately imbalanced. The imbalances are due to the low number of patients (177) in the platinum-based chemotherapy +/- pemetrexed arm relative to the number of population characteristics that are targeted to be balanced in conjunction with the existing differences in these variables at baseline. The imbalances between characteristics after weighting cast doubt on the validity of results and will likely lead to a bias in the hazard ratio and any other estimates resulting from this analysis.

Table 6: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given platinum-based chemotherapy +/- pemetrexed in pre-treated setting with adjustment

	Level	Platinum-based chemotherapy	Pralsetinib	SMD	Adjusted
Age (%)	< 65	[redacted]	[redacted]	0.291	Y
	>= 65	[redacted]	[redacted]		
Sex (%)	F	[redacted]	[redacted]	0.17	Y
	M	[redacted]	[redacted]		
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	0.431	Y
	No history of smoking	[redacted]	[redacted]		
ECOG (%)	0	[redacted]	[redacted]	0.128	Y
	1	[redacted]	[redacted]		
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.038	Y
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.169	Y
	STAGE IV	[redacted]	[redacted]		
Race (%)	White	[redacted]	[redacted]	0.178	Y
	Other	[redacted]	[redacted]		
	Unknown	[redacted]	[redacted]		

		Sum of total metastases (median [IQR]) | | [redacted] | [redacted] | 2.403 | N **Metastases (%)** | Isolated brain/CNS site | [redacted] | [redacted] | 2.787 | N None | [redacted] | [redacted] Other | [redacted] | [redacted] **Brain/CNS metastasis only (%)** | 0 | [redacted] | [redacted] | 0.721 | N 1 | [redacted] | [redacted] **Liver metastasis only (%)** | 0 | [redacted] | [redacted] | 0.304 | N 1 | [redacted] | [redacted] Pralsetinib demonstrates a trend of improved OS (HR [redacted], 95% CI [redacted]) compared to platinum-based chemotherapy +/- pemetrexed, though the result is not significant at the 5% level. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted]). However, due to the imbalances that remained after adjustment, the comparison was not considered suitable to inform the current appraisal. The motivation for using Flatiron EDM data was the availability of individual patient level data to inform an adjustment in the comparator arm in order to reflect characteristics of a *RET* fusion-positive population. Propensity score matching was also used with similar results as those from weighting. Thus, given in this comparison a sufficient adjustment was not feasible, a naïve comparison represented the most roust methodology available to estimate comparative efficacy of pralsetinib vs. platinum-based chemotherapy +/- pemetrexed in the pre-treated setting (Company Submission, Section B.2.9.4, page 67-80).
Key issue 7. No correction for crossing curves in probabilistic sensitivity analysis	No	This issue was resolved by the ERG as part of the technical engagement process. As per the Technical Engagement Clarification Call (17th November 2021), no further action is required on this issue.

Key issue 8. Constant benefit of pralsetinib assumed without justification and based on immature data	Yes	*Context of treatment waning* Consistently, the topic of a potential waning of treatment effect in NICE oncology appraisals is subject to great uncertainty. In order to design a clinical trial to demonstrate a continued and statistically significant treatment effect benefit at 2, 3, 4, 5 years, the number of subjects needed to be recruited would have to be substantially higher. It would lead to trial delays to recruit the number of patients required (exacerbated by the fact this is a rare mutation) and further delays to wait for trial results to read out. This would result in substantial delays to patient access which would likely be considered undesirable. Therefore, providing clinical trial evidence to adequately test this hypothesis and provide evidence on the exact degree of treatment waning is not feasible and would likely be considered undesirable for patients. Although it is not feasible to provide statistically significant clinical trial evidence, we are able to provide evidence to suggest at the potential likelihood of treatment waning in the remainder of this response. Further, Roche note that the cost-effectiveness results are not sensitive to assumptions surrounding treatment waning for PFS and TTD. In the updated company base case, the difference in the incremental cost-effectiveness ratios (ICERs) between ERG preferred assumptions on PFS/TTD treatment waning and no PFS/TTD treatment waning is [redacted]% across all pairwise comparisons. Therefore, for simplicity the remainder of this response will focus only on treatment waning for OS and assume no treatment effect waning in PFS and TTD. *Treatment effect vs comparators including pembrolizumab in the untreated setting* Treatment effect (and any potential waning) is relative to the comparator treatments. In the UK untreated setting, both comparators include pembrolizumab and therefore patients are not on treatment after 2 years due to a stopping rule for pembrolizumab. Therefore, in the untreated setting, treatment waning and a stopping rule on treatment effect enforces the assumption that after a given time point there is no clinical benefit to treatment with pralsetinib over no treatment at all. However, this stopping rule is not in place in the United States and therefore this effect will not be seen in the observed data.

		Treatment effect in the observed data In both the untreated and the pre-treated population for pralsetinib there is observed OS data for [redacted] months (Company submission, Section B.2.6.3, Figures 12-13, pages 61-62). However, limited inferences should be drawn from the tails of the curves since the number of patients at risk is low. In the untreated population, there are only [redacted] patients at risk from [redacted] months onwards. In the pre-treated population, there are only [redacted] patients at risk from [redacted] months onwards. For the untreated population, it is possible to examine the relative treatment effect in the observed data by assessing the proportional hazards tests, including the log-negative-log plots (Clarification question C4d response, Figures 3-4, pages 57-69). For the observed data for pralsetinib in comparison to both pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy, there is a continued widening of the treatment effect. In the pre-treated population we are able to use the OS Kaplan-Meier curves to assess the potential treatment waning (Company Submission, Section B.2.9.4, Figures 19, 21, 23, pages 76-78). In all three cases there is a clear and continued widening of the curves between the pralsetinib OS curves and comparators suggesting no waning of treatment effect in this period. In both populations, OS treatment effect not only appears to not wane, but it appears to widen as time goes on within the observed period. The evidence suggests that there is no waning of the treatment effect in the observed period where there are a reasonable number of patients at risk in the pralsetinib arm. Therefore, the ERG exploratory analysis can be considered implausibly conservative given this assumes that treatment waning begins at 12 months as this is contrary to the observed data. *Implied treatment effect from clinical experts landmark survival predictions* One potential source of evidence to assess the likelihood of potential OS treatment effect waning is to use clinical expert's landmark OS predictions for each treatment to make inferences regarding the duration of the treatment effect for pralsetinib compared to comparators. By calculating the conditional survival from one landmark OS prediction to the next, we are able to infer clinical expert's predictions on the relative treatment effect of pralsetinib vs. comparators and therefore comment on potential treatment waning. An identical conditional survival from one landmark to the next would suggest no

treatment effect. A higher conditional survival in the pralsetinib arm compared to comparators would suggest that clinical experts expect a continued OS treatment effect.

In the untreated setting, clinical experts predict that the conditional survival from 0-3 years and then 3-5 years is higher in the pralsetinib arm vs. comparators. The relative increase is higher in the 3-5 year period compared to 0-3 year period which would suggest no waning of OS treatment effect in the first 5 years of the model and potentially a widening of the OS treatment effect. In the 5-10 year period, the conditional survival in the pralsetinib arm is equal to or lower than comparators.

In the pre-treated setting, conditional survival in the 0-3 year period, 3-5 year period and 5-10 year period is higher in the pralsetinib arm vs. comparators. This would suggest that clinical experts estimate no waning of treatment effect across this time period.

Table 7: Clinical expert landmark survival estimates and implied estimated conditional survival estimates for pralsetinib and comparators in untreated and pre-treated setting

	3 years	5 years	10 years	Conditional survival from 0-3 years	Conditional survival from 3-5 years	Conditional survival from 5-10 years
Untreated						
Pralsetinib	50%	40%	10%	50%	80%	25%
Pembrolizumab + pemetrexed + chemotherapy	30%	10%	4%	30%	33%	40%
Pembrolizumab monotherapy	25%	8%	2%	25%	32%	25%
Pre-treated						
Pralsetinib	35%	20%	7%	35%	57%	35%
Docetaxel monotherapy	5%	2%	0%	5%	40%	0%

Docetaxel + nintedanib	5%	2%	0%	5%	40%	0%
Platinum-based chemotherapy +/- pemetrexed	15%	5%	1%	15%	33%	20%

*Due to extremely small proportions of patients alive at the 20 year mark, it was not considered reliable to include conditional survival from 10-20 years in the analysis

However, it should be acknowledged that clinical experts stated they found the task of estimating landmark survival extremely difficult. These results would be sensitive to small changes in clinician's estimates. Especially given estimates are often rounded to the nearest multiple of 5/10 for simplicity which may impact results. Therefore, this methodology cannot be considered robust. Merely, it is an attempt to address an uncertainty in the data where providing robust long-term evidence is not possible.

Treatment effect in comparable appraisals

In previous appraisals in comparable populations for entrectinib and selpercatinib, no waning of OS treatment effect was modelled in the final model assumptions approved by the committee.(11, 12)

Scenarios exploring varying treatment waning

A number of different treatment waning assumptions and the impact on the ICER was assessed in Table 8. The various assumptions represent the full range of what can be considered realistically plausible assumptions. The ERG's base case assumption is that treatment waning begins soon after or at the exact point that the observed data for pralsetinib finishes ends. This should be considered as a conservative bound for the plausible range of treatment waning scenarios. The ERG's scenario analysis on treatment waning assumes treatment waning begins at the 1-year period. This is not reflected in the observed data and should not be considered in the range of plausible assumptions. Overall, results are not sensitive to assumptions on treatment waning with a relatively small range between the most optimistic and pessimistic assumptions. The results of the cost-effectiveness analysis are not sensitive to OS treatment waning assumptions. Given the paucity of robust long-term OS evidence, it is not

possible to comment confidently on whether there will be a potential waning of OS treatment effect and if so, to what extent that would be. In order to maintain consistency with what was approved by the committee in comparable previous appraisals, the company base case assumes no waning of the OS treatment effect.

Table 8: Scenarios explore impact of varying assumptions on waning OS treatment effect on ICER for pralsetinib (with PAS) vs. untreated and pre-treated comparators

Pralsetinib vs.	ICER (£/QALY) with OS treatment effect waning starting at 2 years and lasting for 3 years	ICER (£/QALY) with OS treatment effect waning starting at 3 years and lasting for 3 years	ICER (£/QALY) with OS treatment effect waning starting at 5 years and lasting for 0 years	ICER (£/QALY) with OS treatment effect waning starting at 5 years and lasting for 5 years	ICER (£/QALY) with no OS treatment effect waning
Pembrolizumab + pemetrexed + chemotherapy (untreated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy (untreated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy (pre-treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib (pre-treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		pemetrexed (pre-treated) | | | | | | ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14 *Conclusion* • Given the difficulties in estimating long-term waning of treatment effect in oncology appraisals, uncertainties are common • There is no evidence of the beginning of the waning of the treatment effect in the observed data (with sufficient number of patients at risk up to [redacted] months in the untreated setting and [redacted] months in the pre-treated setting) • Inferences from clinical experts' landmark OS predictions estimate that they do not believe there will be treatment waning in the first 5 years of treatment although results cannot be considered robust • No treatment waning was assumed in the two NICE appraisals most comparable to this one • The full range of plausible scenarios have been explored in Table 8. The impact on cost-effectiveness results is not substantial. For consistency with previous appraisals, the company base case assumes no waning of the OS treatment effect
Key issue 9. Substantial uncertainty in survival curve extrapolations due to immaturity of data	No	*Context of data immaturity* Roche acknowledge a degree of immaturity in the ARROW data. This is a natural consequence of working in a rare mutation such as *RET* which makes recruitment for trials more problematic and therefore limits trial sample size. Further, the low number of events over the [redacted] months of follow up across the untreated and pre-treated settings has resulted in patients' survival being modelled predominantly in the unobserved period in the economic model. This is especially true in the case of OS.

		In terms of sample size and maturity of data, the current appraisal is comparable and in some instances favourable to previous NICE appraisals in advanced NSCLC in rare mutations (entrectinib and selpercatinib).(11, 12) *Curve selection* In all cases of curve selection, NICE guidance and best practice was followed to ensure curve selection was as robust and systematic as possible so as to mitigate the impact of curve selection and immaturity of data on results.(13, 14) The ERG note some disparities between clinical expert landmark survival predictions and model predictions (ERG report, Section 4.2.6.11, page 92-93). At the upper end of disparities, absolute over/under prediction ranges from 5-11%. It should be noted that clinical experts in the advisory board expressed great difficulty at accurately placing numerical survival values at landmark points. Further, clinical experts were not simultaneously shown the observed data whilst being asked to make landmark predictions. Therefore, this may lead to some potential inconsistencies between the observed data and the early (e.g. 3-year) landmark survival predictions. The 3-year landmark survival periods are slightly past the end of the observed period where minimal extrapolation has occurred. Clinical experts were shown the predicted HRs from the indirect treatment comparison and commented that they are likely to be observed in clinical practice. Therefore, Roche feel that in this context, absolute errors of 5-11% in some sections of the extrapolation represent an acceptable range of error. The ERG also quote relative over/under prediction of model landmark survival compared to clinical expert predictions. Roche believe that in terms of impact on overall results, the absolute values should take precedence. For example in the hypothetical case of an over prediction of 2% vs 1%, the relative over prediction is 100% which would allude to a large difference however due to the low absolute numbers of patients alive the impact on model results is likely to be minimal. The ERG state "*as it was difficult to identify curves that were optimal for both pralsetinib and comparators, in particular for the untreated population, the ERG refrains from replacing the distributions in the ERG preferred assumptions*" (ERG report, Section 4.2.6, page 93). Roche note that the ERG

		have not proposed new curve selections. Roche propose that, having followed NICE guidance, in the current context, the current curve selections represent the most robust methodology available to model survival. *ERG calibration approach* Roche note the ERG's scenario of the calibration approach where HRs are calibrated based on clinical experts landmark survival predictions at the 3-year period. This is very sensitive to clinical experts predictions which clinicians stated to be a difficult exercise and were often rounded to multiples of 5/10 and can therefore considered to be approximations instead of an exact science which when translated into HRs can impact results. Roche suggest this is an inferior and less robust methodology than the systematic ITC conducted in the company submission which includes observed data from clinical trials and real world evidence datasets. Given there is a disparity between the HRs from the ITC and the ERG calibrated approach and the ITC outputs were shared with clinical experts at the same advisory board who deemed them to be realistic, the extent to which the ERG calibration approach should be considered in relation to decision making is questionable. *Future evidence* The issue of immaturity in the untreated population will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of *RET* fusion-positive, advanced NSCLC. EQ-5D will be collected in the trial. Recruitment is expected to be completed in [redacted] with results expected in [redacted].
Key issue 10. Adverse event incidences included in the model potentially subject to error	Yes	*Pralsetinib* The inconsistency in sample sizes of the safety populations between those presented in the Company Submission was not an error but relates to the different ARROW trial populations used in each section.

		The safety population presented in the clinical section (Company Submission, Section B.2.10.2, Table 28, page 98) represents the published MDP population which remains consistent with the rest of the clinical section. The safety population presented in the economic section (Company Submission, Section B.3.3.3, Table 55, page 150) represents the safety/unrestricted efficacy population and was used in the model to align to the population used for efficacy in the same model. In the pralsetinib untreated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. In the pralsetinib pre-treated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. Therefore, the impact of the selection of either ARROW trial population to use for adverse events in the economic model on cost-effectiveness results is negligible. *Comparators* With regards to comparators, there were some typographical errors in the reporting of the published sources used for adverse event incidence in the Company Submission (Section B.3.3.3, Table 55, page 150) and economic model. • In the case of pembrolizumab monotherapy, the correct reference was provided in the Company Submission but the Company Submission and the economic model both incorrectly report the adverse event incidence of as pneumonia 7% whereas, as per the published source, it should be pneumonia 0% and pneumonitis 3%. This has been updated in Table 9 and the accompanying economic model "ID3875_Pralsetinib for *RET* fusion-positive advanced NSCLC_CEM_TE_ACIC". • In the case of docetaxel monotherapy, the Company Submission incorrectly referenced Mazieres. (15) The adverse event incidences provided in the Company Submission and economic model represented those provided by Rittmeyer. (16) This has been updated in Table 9. There is no impact on cost-effectiveness results. • In the case of platinum-based chemotherapy +/- pemetrexed, the Company Submission correctly referenced Ardizzoni. However, the adverse incidences provided in the Company Submission and economic model were incorrectly reported. These have been updated in Table

9 and the accompanying economic model "ID3875_Pralsetinib for *RET* fusion-positive advanced NSCLC_CEM_TE_ACIC".

In the case of pembrolizumab + pemetrexed + chemotherapy and docetaxel + nintedanib, the sources and adverse events presented in the Company Submission align to those used in the economic model and therefore no updates were made.

Table 9: Adverse events included in the economic model (Company Submission, Section B.3.3.3, Table 55, page 150)

	Untreated			Pre-treated			
n, (%)	**Pral**	**Pembro + chemo**	**Pembro mono**	**Pral**	**Doce mono**	**Doce + nin**	**PBC +/- pem**
	ARROW	**(17)**	**(18)**	**ARROW**	**(16)**	**(19)**	**(20)**
	n=404	**n=405**	**n=636**	**n=404**	**n=578**	**n=652**	**n=112**
Anaemia	[redacted]	74 (18)	0 (0)	[redacted]	33 (6)	0 (0)	6 (5)
Asthenia	[redacted]	27 (7)	0 (0)	[redacted]	13 (2)	13 (2)	0 (0)
Blood creatinine phosphokinase increased	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Decreased appetite	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Decreased neutrophils	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	209 (32)	0 (0)
Decreased white blood cell count	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	107 (16)	0 (0)
Diarrhoea	[redacted]	21 (5)	0 (0)	[redacted]	0 (0)	43 (7)	0 (0)
Disease progression	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Dyspnoea	[redacted]	17 (4)	0 (0)	[redacted]	14 (2)	32 (5)	0 (0)
Fatigue	[redacted]	28 (7)	0 (0)	[redacted]	23 (4)	37 (6)	6 (5)
Febrile neutropenia	[redacted]	0 (0)	0 (0)	[redacted]	62 (11)	46 (7)	3 (3)
Hepatitis	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Hyperglycaemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Hypertension	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Hypocalcaemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Hyponatraemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	14 (2)	0 (0)
Hypophosphataemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)

Increased ALT	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	51 (8)	0 (0)
Increased AST	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	22 (3)	0 (0)
Leukopenia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	19 (3)	9 (8)
Lymphocyte count decreased	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Lymphopenia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Malignant neoplasm progression	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Nausea	[redacted]	14 (3)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Neutropenia	[redacted]	65 (16)	0 (0)	[redacted]	75 (13)	79 (12)	13 (12)
Pain	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Pleural effusion	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Pneumonia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	20 (3)	0 (0)
Pneumonitis	[redacted]	12 (3)	20 (3)	[redacted]	0 (0)	0 (0)	0 (0)
Rash	[redacted]	8 (2)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Sepsis	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Severe skin reactions	[redacted]	9 (2)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Thrombocytopenia	[redacted]	34 (8)	0 (0)	[redacted]	0 (0)	0 (0)	9 (8)
Urinary tract infection	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Vomiting	[redacted]	16 (4)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

The impact of the above changes on cost-effectiveness results are presented in Table 10. The changes reduce the ICERs, although the impact can be considered negligible.

Table 10: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared to pembrolizumab monotherapy (untreated) and platinum-based chemotherapy +/- pemetrexed (pre-treated) before and after updated adverse event incidences

Pralsetinib vs.	ICER (£/QALY) before adverse event incidence update outlined in response to Key Issue 10	ICER (£/QALY) after adverse event incidence update outlined in response to Key Issue 10
Pembrolizumab monotherapy (untreated	[redacted]	[redacted]

		Platinum-based chemotherapy +/- pemetrexed (pre-treated) | [redacted] | [redacted] ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14
Key issue 11. Lack of direct evidence to inform health-related quality of life	Yes	*Summary* Roche acknowledge a degree of uncertainty given utilities were not able to be informed from trial outcomes and there were no existing *RET* fusion-positive advanced NSCLC in the published literature or previous NICE appraisals. This is an unfortunate downside of working in a rare mutation such as *RET.* In this context, we proposed that the best solution is to use health state utility values that have been previously approved by NICE committees in appraisals in patient populations which represent the most comparable to the current appraisal. We note that the ERG report does not suggest any alternative approaches which may indicate that, given the current evidence base with existing uncertainty, they agree that this is the best available approach. Therefore, in the updated company base case, the health state utility values remain as per the initial company submission. *Untreated health state utility values* The ERG reports that the company submission is lacking in explanation for the choice of proxies for the untreated population. We agree that potentially all three sources/populations could arguably represent suitable proxies. All three populations were approved by previous committees to be the best available evidence to represent their populations. All three populations represented are comparable to the target *RET* population in this appraisal. As demonstrated in the Company Submission scenario analysis (Section B.3.8.3, Table 84, page 193-4), we note that the ICER is not sensitive to the selection of the utility proxy. Results have been updated with the updated company base case in Table 11 for the untreated population. The selected

proxies in the company base case were chosen as they represent the most comparable population to *RET* and also represented the scenario with utilities with ICERs in the middle of the range.

Table 11: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared untreated comparators with varying sources for health state utility values

Pralsetinib vs.	ICER (£/QALY) updated company base case (PF: 0.794, PD: 0.678)	ICER (£/QALY) Using alternative utility scenario (21) (PF: 0.784, PD: 0.725)	ICER (£/QALY) Using alternative utility scenario (22) (PF: 0.780, PD: 0.660)
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14

Pre-treated health state utility values

Roche note the ERG's comment (ERG report, Section 4.2.8, page 97) that the PD health state utility value in the pre-treated population (0.628) is debateable, as it was in ID3743. The value of 0.628 represents a mid-point between the health-related quality of life data collected in LIBRETTO-001 (0.688) and the value approved in TA713 (0.569) (ID3743 Appraisal consultation document, Section 3.13, page 13). (1)

[redacted]

		[redacted] Further, we note that results are not sensitive to the choice of proxy chosen (Table 12). **Table 12: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared pre-treated comparators with varying sources for health state utility values** **Pralsetinib vs.** / **ICER (£/QALY) updated company base case (PF: 0.713, PD: 0.628)** / **ICER (£/QALY) Using alternative utility scenario (22) (PF: 0.853, PD: 0.659)** / **ICER (£/QALY) Using alternative utility scenario (11) (PF: 0.672, PD: 0.653)** **Docetaxel monotherapy** [redacted] **Docetaxel + nintedanib** [redacted] **Platinum-based chemotherapy +/- pemetrexed** [redacted] ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14 *Future evidence* The health state utility evidence gap in the untreated population will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of RET fusion-positive, advanced NSCLC. EQ-5D will be collected in the trial. Recruitment is expected to be completed in [redacted] with results expected in [redacted].
Are there any important issues that	No	--

have been missed in ERG report?		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 13: Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Inclusion of patient's previously treated with a *RET* inhibitor	Section 4.2.3, page 85	No	The ERG report states the population in the economic evaluation is not fully in line with the NICE scope as it does not include patients previously treated with a *RET* inhibitor. Since marketing authorisation is line-agnostic, this group should be included in the economic evaluation. As outlined in the Company Submission (Section B.1.1, page 12). The recent EMA marketing authorisation for pralsetinib does not include patients previously treated with a *RET* inhibitor. "*Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated*

			with a RET inhibitor" The MHRA licence is anticipated via the EU reliance route and is therefore expected to mirror the above wording. Therefore, the population used in the economic evaluation is reflective of the anticipated marketing authorisation and no amendments will be made to the population used in the economic evaluation. Further, the ERG report states it was not clear how the company excluded patients previously treated with a *RET* inhibitor from the model inputs such as clinical effectiveness, AEs, costs and HRQoL. In the ARROW trial, subjects in Group 6 were previously treated with a *RET* inhibitor. Trial data was used for clinical effectiveness and AEs only in the base-case economic model. ARROW data used in the economic model did not include Group 6 subjects to ensure that the economic model aligned with the marketing authorisation.
Additional issue 2: Time on treatment falling below PFS for pralsetinib in the untreated population	Section 4.2.6.11, page 93	No	The ERG report notes a separation between the PFS and TTD curves in the respective tails of the untreated population. The ERG hypothesises that this is either because 1) an artefact in the data because of small sample size and immaturity or 2) patients were indeed taken off treatment before progression because of an implicit stopping rule.

			Roche note that in the graph in question (ERG Report, Figure 4.2, page 94), PFS and TTD closely follow each other for the first [redacted] months of the respective Kaplan-Meier curves. It appears the separation that the ERG is referencing is after the [redacted] month period where there are very few patients at risk (e.g. [redacted] patients at risk in the PFS curve). Indeed, the separation appears to be from just [redacted] subjects who discontinued treatment before progression. Of the two options presented by the ERG, provided a low number of events is driving this, it would allude to option 1) (an artefact in the data because of small sample size and immaturity). Roche would caution inferring too much from a small number of events. The small sample size and immature data is in itself an artefact of working in a rare mutation such as *RET*. Roche note the preference of the committee in the selpercatinib appraisal to use TTD to model treatment costs for selpercatinib (Selpercatinib Appraisal Consultation Document, Section 3.11, page 13-15).
Additional issue 3: Pre-treated supportive care costs	Section 4.2.9.10, page 101-2	Yes	Roche recognises the ERG's concerns regarding the implied inconsistencies in the company approach whereby utilities are lower in the pre-treated setting compared to the untreated setting and health care costs are identical. To address this, the company base case has been updated to arbitrarily assume pre-treated PF supportive care costs are equal to

<table>
<tr><td></td><td></td><td></td><td colspan="2">untreated and pre-treated PD supportive care costs (£227.01).

The difference between PF and PD supportive care costs is minimal (£202.22 vs. £227.01). The impact of this updated on ICERs in the pre-treated setting is displayed in Table 14 and can be considered negligible.</td></tr>
<tr><td>Additional issue 4: Relative dose intensity</td><td>Section 4.2.9.10, page 102</td><td>Yes</td><td colspan="2">Currently, the scenario assumes 100% relative dose intensity for pralsetinib and based on a previous submission for sotorasib, a 90% relative dose intensity for comparators.

Roche have amended the ERG's relative dose intensity scenario analysis below. For pralsetinib, Roche propose the relative dose intensity should be [redacted] (CSR, page 140). For pembrolizumab, Roche propose the relative dose intensity should be 95.6% (NICE TA683, Clarification question B5, page 35). (23) For other comparators including chemotherapy, Roche propose relative dose intensity should be 96.4% (NICE TA683, Clarification question B5, page 35).

In the case of pralsetinib, pembrolizumab and chemotherapy, these relative dose intensities are taken directly from trials and can be considered more robust than the ERG's assumptions.</td></tr>
<tr><td></td><td></td><td></td><td>ICER pral vs. (untreated)</td><td>ICER pral vs. (pre-treated)</td></tr>
</table>

			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
			Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14 The ICERs presented above are lower than those presented in the ERG scenario analysis and in the company base case. Roche have made the conservative assumption to not include relative dose intensity in the updated company base case.	
Additional issue 5: Proportion of patients receiving pemetrexed	Section 4.2.9.10, page 102	No	The ERG report states there is a lack of justification for the proportion of 63% receiving pemetrexed in the platinum-based chemotherapy +/- pemetrexed comparator. This figure is estimated from an average of feedback from clinical experts in the advisory board. Clinicians were asked to estimate the proportion of *RET* fusion-positive patients in the PD-L1>50% pathway receiving who would go on to receive each of the available treatments in the NICE pathway. The estimate of 63% represents the proportion of patients receiving platinum-based chemotherapy with pemetrexed (including for maintenance) divided by the total proportion of patients receiving platinum-based chemotherapy with or without pemetrexed (including for maintenance). Given this feedback was	

			received from clinical experts, Roche believe this is representative of UK clinical practice. The study used to inform efficacy includes 100% of patients receiving pemetrexed. Therefore, the efficacy benefits of pemetrexed are included for 100% of patients (which is not representative of UK practice). However the costs of pemetrexed are included for only 63% of patients (which is representative of UK practice. Therefore, Roche consider this to be a conservative approach.
Additional issue 6: Testing rate used in scenario analysis	Section 4.2.9.10, page 102	No	The ERG states "*the ERG is unclear what the company exactly means with the proportion of test costs due to pralsetinib, which was arbitrarily set at* [redacted]" The costs of *RET* fusion testing that should be attributed towards pralsetinib in the economic model in this appraisal should represent the extent to which the potential approval of pralsetinib by NICE would increase *RET* fusion testing costs. As per the Company Submission (Section B.3.5.5, page 166-7), The Department of Health and NHSE&I have outlined their NHS Long Term Plan where they have committed to offer whole genome sequencing routinely (500,000 whole genomes) by 2023-24. Therefore the company base case assumes the potential approval of pralsetinib by NICE will have no impact on *RET* testing costs. The testing scenario presented by the company was

			meant to explore the impact of assuming there was some impact of the potential approval of pralsetinib on testing costs. It is difficult to put a percentage figure on this, therefore the figure of [redacted] arbitrarily represents a scenario where the potential approval of pralsetinib increased testing costs by the amount of [redacted] of total patients being tested. The scenario was selected to mirror a key issue in the selpercatinib appraisal. As part of that appraisal, NHSE provided a suitable cost per test to the company which the company accepted and included as part of the economic model (Selpercatinib Appraisal Consultation Document, Section 3.12, page 15). This cost was not presented but it was commented in the committee meeting that the impact of the introduction of this testing cost on results was negligible.
Additional issue 7: End-of-life, life extension criterion in untreated setting	Section 7, page 122	No	The evidence packaged presented for pralsetinib justifies meeting the life extension criterion in the untreated setting. The ERG report suggests that this is not met due to issues 2, 4 and 5. Issue 2 relates to the selection of comparators which has been addressed in the relevant section of Table 2. Issue 4 relates to the SLR which is only relevant for the pre-treated setting and not relevant for the indirect comparisons in the untreated setting as the Flatiron EDM dataset was used to inform comparator efficacy in the untreated setting. Issue 5 relates to safety has already been

			addressed in the relevant section of Table 2. To determine the extent to which pralsetinib extends life over the untreated comparators and therefore meets the life extension criterion, the relevant section of the submission is the untreated indirect treatment comparison for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy (Company Submission, Section B. 2.9.5). Roche note that in Section 3.4 ERG report there was minimal critique of this comparison which seemed to imply confidence in the approach taken. Further, the ERG note that to demonstrate the second criterion is met "*robust comparative data must be provided whereas no MAIC was performed (see Key issue 2)*" (ERG Report, section 7, page 122). This is confusing given in the untreated comparison propensity scoring using IPD has been conducted which, in the ERG's own words is "*superior*" (ERG Report, Section 3.3, page 63) to a MAIC. In the updated company base case, economic model estimates patients in the untreated setting who receive pralsetinib have an undiscounted life expectancy of [redacted] months. This represents a life extension of [redacted] months and [redacted] months over pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy respectively. This is substantially more than the 3 month life extension required to meet the criterion.

			Clinical experts consulted by Roche in an advisory board were in agreement that pralsetinib would extend life by substantially more than 3 months.
Additional issue 8: End-of-life, life extension criterion in pre-treated setting	Section 7, page 122	No	The evidence packaged presented for pralsetinib justifies meeting the life extension criterion in the pre-treated setting. The ERG report suggests that this is not met due to issues 2, 4 and 5. Each of these issues have been addressed in the responses in relevant sections of Table 2. In the updated company base case, economic model estimates patients in the pre-treated setting who receive pralsetinib have an undiscounted life expectancy of [redacted] months. This represents a life extension of [redacted] months over pre-treated comparators. This is substantially more than the 3 month life extension required to meet the criterion. Further, the ERG note that to demonstrate the second criterion is met "*robust comparative data must be provided whereas no MAIC was performed (see Key issue 2)*" (ERG Report, section 7, page 122). This is confusing given in the pre-treated comparison against the primary comparator (docetaxel monotherapy), propensity scoring using IPD has been conducted which, in the ERG's own words is "*superior*" (ERG Report, Section 3.3, page 63) to a MAIC. Clinical experts consulted by Roche in an advisory

			board were in agreement that pralsetinib would extend life by substantially more than 3 months.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 14: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
--	--	--	**Submission base case ICER, pral vs. (untreated)**	**Submission base case ICER, pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
Key issue 7: PFS vs. OS fix	Without ERG fix	With ERG fix of PFS < OS	No change to base case results	
Key issue 10: Adverse event inconsistencies	As per company submission	As outlined in response to key issue 10 (with typographical errors fixed)	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]

			--	PBC +/- P: [redacted]
Additional issue 3: Pre-treated PD supportive care costs	£202.22	£227.01	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
ERG fix of cisplatin dose (ERG report, Section 4.2.9, page 102)	Without ERG fix for cisplatin dose	With ERG fix of cisplatin dose	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
Company's base case following technical engagement (or revised base case)	--	--	**Updated base case ICER, pral vs. (untreated)**	**Updated base case ICER, pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]

Sensitivity analyses around revised base case

Please see Appendix 3.

Appendix 1: Quality assessment

The ERG report states "*There was no mention of any methodological quality assessment for SLR 2*" (ERG report, Section 3.1.4.2.1, page 45). The quality assessment is provided in Table 15.

Table 15: Quality assessment of SLR 2

Criteria		KEYNOTE-042	KEYNOTE-024	KEYNOTE-189	KEYNOTE-021	OAK	LUME-Lung 1	NVALT7	GOIRC 02-2006
WAS RANDOMISATION CARRIED OUT APPROPRIATELY?	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Unclear**	**Yes**
	Rationale	The randomisation schedule was generated by a computerised randomised list generator	Patients were assigned centrally using an interactive voice response system / integrated web-response system	Patients were assigned using an interactive voice-response and web-response system	Patients were assigned using an interactive voice-response system	Patients were assigned using permute block-randomisation via an interactive voice-response system or web-response system	Patients were assigned using interactive third-party telephone via an interactive voice response system, or web-based randomisation via interactive web-based response system	Method used to assign patients was not reported	Patients were assigned to treatment groups via a minimisation process, through a Web-based system
WAS THE CONCEALMENT OF TREATMENT ALLOCATIO	Decision	**Yes**	**Yes**	**Unclear**	**Unclear**	**No**	**Yes**	**Unclear**	**Yes**
	Rationale	The randomisation schedule was held centrally	The randomisation schedule was held centrally	It was unclear whether the allocation	It was unclear whether the allocation	Allocation was unmasked	Treatment allocation was concealed from	It was unclear whether the allocation	The randomisation schedule was held centrally

Technical engagement response form

N ADEQUATE?				was concealed	was concealed		investigators	was concealed	
WERE THE GROUPS SIMILAR AT THE OUTSET OF THE STUDY IN TERMS OF PROGNOSTIC FACTORS?	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	Rationale	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were generally well balanced between treatment groups†	Demographics and disease characteristics were generally well balanced between treatment groups‡	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups
WERE THE CARE PROVIDERS, PARTICIPANTS AND OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?	Decision	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**Unclear**	**No**
	Rationale	This was an open-label study	This was an open-label study	This was a double-blind trial	This was an open-label study	This was an open-label study	This was a double-blind trial	Method of blinding was not reported	This was an open-label study
	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**Unclear**

WERE THERE ANY UNEXPECTED IMBALANCES IN DROP-OUTS BETWEEN GROUPS?	Rationale	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	Rate of withdrawal was similar between the treatment groups	Rate of withdrawal was similar between the treatment groups	The rate of treatment withdrawal was not reported
IS THERE ANY EVIDENCE TO SUGGEST THAT THE AUTHORS MEASURED MORE OUTCOMES THAN THEY REPORTED?	Decision	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
	Rationale	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias
DID THE ANALYSIS INCLUDE AN INTENTION-TO-TREAT ANALYSIS? IF SO, WAS THIS APPROPRIA	Decision	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
	Rationale	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling	ITT analysis included and appropriate; statistical methods for handling

TE AND WERE APPROPRIATE METHODS USED TO ACCOUNT FOR MISSING DATA?		missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported	missing outcome data were not reported

Abbreviations: ITT, intent to treat.

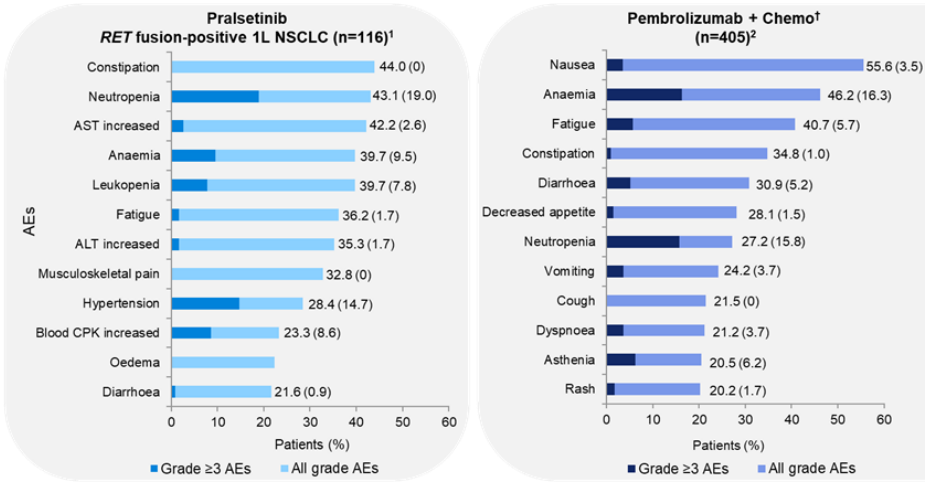
† The percentage of men was higher in the pembrolizumab-combination group than in the placebo-combination group (p=0.04).

‡ Proportionally, more women were enrolled than men (63% of patients in the pembrolizumab plus chemotherapy group and 59% of patients in the chemotherapy group were women).

Appendix 2: Descriptive analysis of the safety profile of pralsetinib (ARROW) vs pembrolizumab + pemetrexed + chemotherapy (KEYNOTE-189 treatment arms) in 1L NSCLC patients

Acknowledging the need of positioning pralsetinib's safety profile in comparison to standard of care and considering the limitations for a formal indirect comparison, a descriptive analysis shows that pralsetinib presents an alternative safety profile compared to pembrolizumab + pemetrexed + chemotherapy and avoids the immune mediated toxicities associated with checkpoint inhibitors.

Figure 2: Safety profile of pralsetinib compared with pembrolizumab + pemetrexed + chemotherapy (data from Keynote-189 trial)



*Most common AEs defined as ≥20% of patients in the active comparator arm are shown. †In patients with previously untreated metastatic non-squamous NSCLC without EGFR or ALK mutations.

AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate transaminase; Chemo, chemotherapy; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung carcinoma; QD, once daily; RET, rearranged during transfection; SoC, standard of care.

1. Grouped preferred terms were used for anaemia, neutropenia, leukopenia, hypertension, musculoskeletal pain, oedema and fatigue.

2. Gandhi L et al. N Engl J Med 2018;378:2078–2092.

The majority of the most common adverse events reported in ARROW were of mild or moderate intensity (Grade 1/2). Regarding haematologic adverse effects, anaemia was observed with a frequency similar to that in the treatment arms of KEYNOTE-189. Neutropenia was reported more frequently in ARROW than in KEYNOTE-189. Nevertheless, both anemia and neutropenia appeared to be manageable by dose modifications and standard practice measures, as no patient in the 1L NSCLC population of ARROW had to discontinue treatment due to these events.

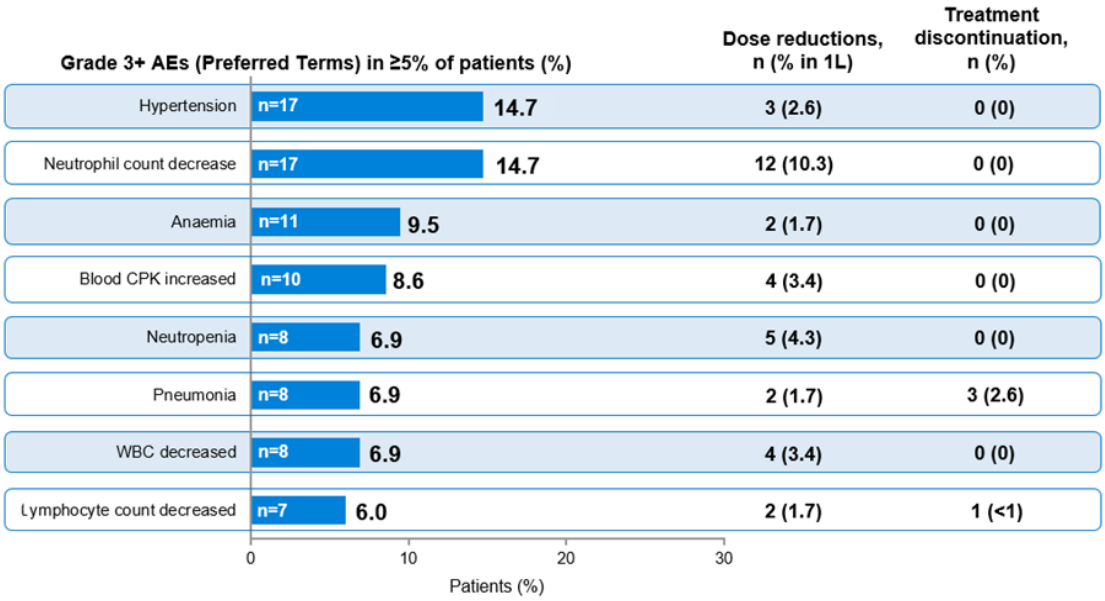
There are three other qualitative differences of note between the pralsetinib safety profile and the KEYNOTE-189 treatment arms in 1L NSCLC: namely hepatic transaminase increases (AST/ALT increased), hypertension and musculoskeletal pain / CPK increase.

- Transaminase elevation observed in ARROW:
    - The vast majority of these events were either Grade 1 or 2
    - No cases of Hy's law or drug-induced liver injury were reported
- Hypertension observed in ARROW:
    - Low rate of patients requiring dose reduction for hypertension
    - No patient needed to discontinue treatment due to hypertension
- Muscular skeletal pain and blood CPK increased observed in ARROW:
    - The events had Grade 1 or 2 intensity in the majority of patient (100% for muscular skeletal pain, 63.0% for blood CPK increase)
    - No patient needed to discontinue treatment due to these events

All of the other events displayed in Figure 2 that were observed after treatment with either pralsetinib or pembrolizumab + pemetrexed + chemotherapy, such as vomiting, occur at similar frequencies across both therapies and are complications of treatment with anti-cancer agents that are routinely managed in the clinic.

In addition, there was a low rate of dose reductions and discontinuations due to grade 3+ events. Dose modifications and standard clinical practice measures enabled the vast majority of patients to continue pralsetinib.

Figure 3: Manageability of grade 3+ events in 1L patients (n=116)



Appendix 3: Updated company base case results

Base-case results

Table 16: Base-case untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 73, page 174

Table 17: Base-case untreated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 18: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab and pemetrexed PAS: ICER (£/ QALY) pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy

	Pemetrexed PAS										
Pembrolizumab PAS	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	[redacted]										
10%	[redacted]										
20%	[redacted]										
30%	[redacted]										
40%	[redacted]										
50%	[redacted]										
60%	[redacted]										
70%	[redacted]										
80%	[redacted]										
90%	[redacted]										
100%	[redacted]										

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 74, page 175

Table 19: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab PAS: ICER (£/ QALY) pralsetinib vs. pembrolizumab monotherapy

Pembrolizumab PAS	ICER (£/ QALY) pralsetinib vs. pembrolizumab monotherapy
0%	[redacted]
10%	[redacted]
20%	[redacted]
30%	[redacted]
40%	[redacted]
50%	[redacted]
60%	[redacted]
70%	[redacted]
80%	[redacted]
90%	[redacted]
100%	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 75, page 176

Table 20: Base-case pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.2, Table 76, page 177

Table 21: Base-case pre-treated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Docetaxel + nintedanib	[redacted]								
Pralsetinib	[redacted]								

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Probabilistic sensitivity analysis

Table 22: PSA untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]							
Pembrolizumab + pemetrexed + chemotherapy	[redacted]							
Pembrolizumab monotherapy	[redacted]							

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1, Table 77, page 177

Table 23: PSA untreated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Pembrolizumab monotherapy	[redacted]								
Pembrolizumab + pemetrexed + chemotherapy	[redacted]								
Pralsetinib	[redacted]								

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 4: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab + pemetrexed + chemotherapy

Figure 5: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.1, Figure 61, page 179

Figure 6: Untreated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years

Corresponding to Company Submission, Section B.3.8.1.1, Figure 62, page 179

Table 24: PSA pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Table 78, page 180

Table 25: PSA pre-treated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 7: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years

Corresponding to Company Submission, Section B.3.8.1.2, Figure 63, page 180

Figure 8: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel + nintedanib

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Figure 64, page 181

Figure 9: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and platinum-based chemotherapy +/- pemetrexed

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Figure 65, page 182

Figure 10: Pre-treated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years

Corresponding to Company Submission, Section B.3.8.1.2, Figure 66, page 182

Deterministic sensitivity analysis

Untreated

Table 26: Untreated DSA for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per first admin.- pemb + pem + chemo	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%

Cost per subsequent admin.- pemb + pem + chemo	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.794	0.780	[redacted]	0.807	[redacted]	95% CI
PD health state utility value	0.678	0.542	[redacted]	0.814	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 79, page 183

Figure 11: Untreated tornado plot for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Figure 67 page 184

Table 27: Untreated DSA for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- pem mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.79	0.78	[redacted]	0.81	[redacted]	95% CI
PD health state utility value	0.68	0.54	[redacted]	0.81	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 80 page 185

Figure 12: Untreated tornado plot for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Figure 68 page 186

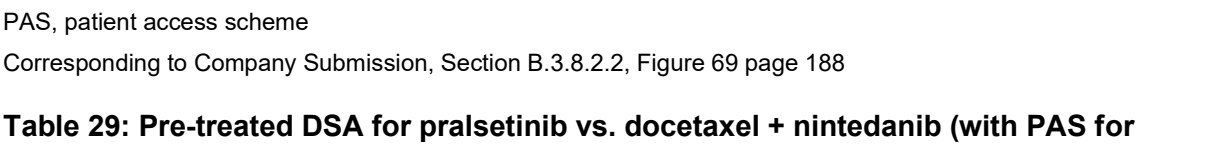
Pre-treated

Table 28: Pre-treated DSA for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.2, Table 81 page 186-187

Figure 13: Pre-treated tornado plot for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)



PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.2, Figure 69 page 188

Table 29: Pre-treated DSA for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib and doce mono	192.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib and doce mono	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce + nin	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%

Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.72	0.71	[redacted]	0.72	[redacted]	95% CI
PD health state utility value	0.63	0.50	[redacted]	0.75	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.2, Table 82 page 188-189

Figure 14: Pre-treated tornado plot for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.2, Figure 70 page 190

Table 30: Pre-treated DSA for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per first admin.- PBC +/- pem	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- PBC +/- pem	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%

Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 79, page 183

Figure 15: Pre-treated tornado plot for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

[redacted]

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.1, Figure 67 page 184

Scenario analysis

Table 31: Untreated and pre-treated scenario analysis

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY) pral vs.		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25-years	5-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – costs and QALYs	3.50%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Half cycle correction	Enabled	Disabled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated OS curve selection for pralsetinib	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated OS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (adjusted IPTW)	As per Flatiron analysis adjusted using matching as per Flatiron technical report (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming no adjustment for metastases)	As per Flatiron analysis assuming adjustment for metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming only ECOG PS 0-1 in eligibility)	As per Flatiron analysis (no ECOG PS restrictions in eligibility criteria)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case	As per naïve comparison (Section B.2.9.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib HRs for OS, PFS, TTD	Assumed equal to docetaxel mono	As per naïve comparison	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method for modelling treatment duration	TTD as per ARROW	Assumed equal to PFS as per ARROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule for pembrolizumab	2-year stopping rule	No stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients in PBC +/- pemetrexed arm receiving pemetrexed	62.8% as per UK clinical practice	100% as per clinical efficacy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion testing costs	Not included	Included as per Section B.3.5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated health state utility values	PF: 0.794 PD: 0.678	PF: 0.784 PD: 0.725	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.794 PD: 0.678	PF: 0.780 PD: 0.660	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated health state utility values	PF: 0.713 PD: 0.628	PF: 0.853 PD: 0.659	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.713 PD: 0.628	PF: 0.672 PD: 0.653	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation
Corresponding to Company Submission, Section B.3.8.2.1, Table 84, page 193-194

Appendix 4: Quantitative bias analysis

Summary of quantitative bias analysis

Roche have recently been exploring quantitative bias analysis in a collaboration with NICE. As part of that collaboration, NICE have requested the inclusion of quantitative bias analysis as part of this appraisal to assess its acceptability and impact on the appraisal

Synthetic control arms are increasingly being used for regulatory and payer submissions involving single arm clinical trials, such as for cancers with rare genetic driver mutations like KRAS and *RET* where a concurrent comparator arm may be infeasible or unethical. (25) Naturally, the possibility that effect estimates or risks can differ systematically between trials and routine clinical practice can be concerning to decision-makers. An approach to mitigate the concerns of bias in non-randomized comparisons is using quantitative bias assessment, which can quantify the strength of plausible sources of biases, such as bias from unmeasured confounding that would be required to nullify or reverse the conclusions of the study. (26) For example, if ECOG status is missing for a large proportion of patients in real-world data, it may be useful to report effect estimates over a range of assumptions about missing ECOG, including non-random missingness. Indeed, the UK NICE has recommended the use of quantitative bias assessment and other sensitivity analyses such as negative/positive controls to support RWE. (27) Although the use of these approaches in non-randomized studies is currently limited, we anticipate that they will see increasing use as pre-specified analyses in the future as interest in RWE inevitably grows. Having done our best to mitigate bias through careful selection and execution of statistical techniques, consider that if the residual bias does not unfairly favour the candidate treatment over the control or standard of care, then the chief question in comparative effectiveness studies can still be answered in a valid manner.

Quantitative bias analysis was conducted on the indirect treatment comparison for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy and pralsetinib vs. pembrolizumab monotherapy in the untreated setting where comparators were informed with data from the Flatiron EDM dataset (Company Submission, Section B.2.9.5, page 80-91).

Quantitative bias analysis for missing data assumptions about baseline covariates

To assess the sensitivity of our results to missing data assumptions, HRs were computed under three scenarios:

1. Baseline confounder data missing completely at random (MCAR) – Using complete case analysis where patients with a missing value for one or more baseline confounders were excluded. Complete-case analysis was used for the main analyses reported in the main document. In the general case for real-world scenarios, MCAR is a simplistic assumption of missingness.

2. Baseline confounder data missing at random (MAR) – Using multiple imputation (MI) of missing data for baseline confounders

3. ECOG PS missing not at random (MNAR) – To account for the robustness of our findings to the non-negligible amounts of missing ECOG performance scores (PS), using multiple imputation with delta adjustment (see below), where missing data for baseline confounders was imputed under the assumption that patients with a missing ECOG PS in the comparator arm to pralsetinib could have been poorer than expected under MAR, and therefore explained away some of the observed differences in outcomes.

MAR and MNAR analyses required multiple imputation, which was performed using chained equations.(28) For multiple imputation, 20 imputed datasets were generated to account for uncertainty and random error in the prediction of missing values. N=20 was chosen to balance computational efficiency with theoretical guidelines for multiple imputation from Graham et al given the proportion of missing values in our data.(29) Predictive mean matching and logistic regression were used to impute

continuous and dichotomous variables except ECOG PS, which used ordered proportional-odds logistic regression. For congeniality, all variables used in propensity score estimation and Cox regression were included in multiple imputation, including outcome variables. Mean observed ECOG PS at any time was included as auxiliary variables to improve prediction accuracy. HRs and standard errors were computed for each imputed dataset separately and then pooled using Rubin's rules to account for intra- and inter-imputed dataset variance.(30) For median survival times, simple mean values for 95% CI were calculated.

For δ adjustments, δ was an additive term applied to the ordered logistic regression model for ECOG PS representing $\log \frac{p(Y \leq j)}{p(Y>j)}$. (31, 32) For the adjustments, fixed constant values of δ of 1, 0, -1, -2, -3, -4 and -5 were added to the ordered logistic regression imputation model for ECOG PS. As shown in Figure 16, positive values for δ probabilistically shifted predicted ECOG PS to be more favourable than expected under MAR, i.e., assigning a lower ECOG PS than predicted given observed covariates, for those missing ECOG PS. Conversely, a negative δ randomly shifted predicted ECOG PS to be poorer than expected under MAR.

Twenty datasets were multiply imputed for each setting of the δ parameter. At δ=-3, for example, amongst those in the pembrolizumab arm lacking baseline PS (approximately 23% of all patients), only 4% of patients were predicted to have an ECOG PS of 0, as opposed to 18% amongst all patients with a non-missing ECOG PS. For interpretability of results, instead of the log-odds defined by δ, we report the resulting mean shift in imputed ECOG PS for each setting of δ. The delta value of zero represents standard multiple imputation.

Table 32: Hazard ratios comparing pralsetinib vs pembrolizumab monotherapy and pralsetinib vs pembrolizumab + pemetrexed + chemotherapy using multiple imputation. Consistent with eligibility criteria for this study, patients with imputed ECOG PS >1 were excluded

Exposure	Reference	HR
Pralsetinib (n=71)	Pembrolizumab (Mean n=920)	[redacted]
Pralsetinib (n=71)	Pembro + chemo (Mean n=1635)	[redacted]

Figure 16: Distribution of ECOG PS by delta (δ). Note that the sample sizes for patients includes those with both missing and non-missing baseline ECOG PS, but for the analyses, patients with ECOG PS >1 were excluded as this was an eligibility criterion.

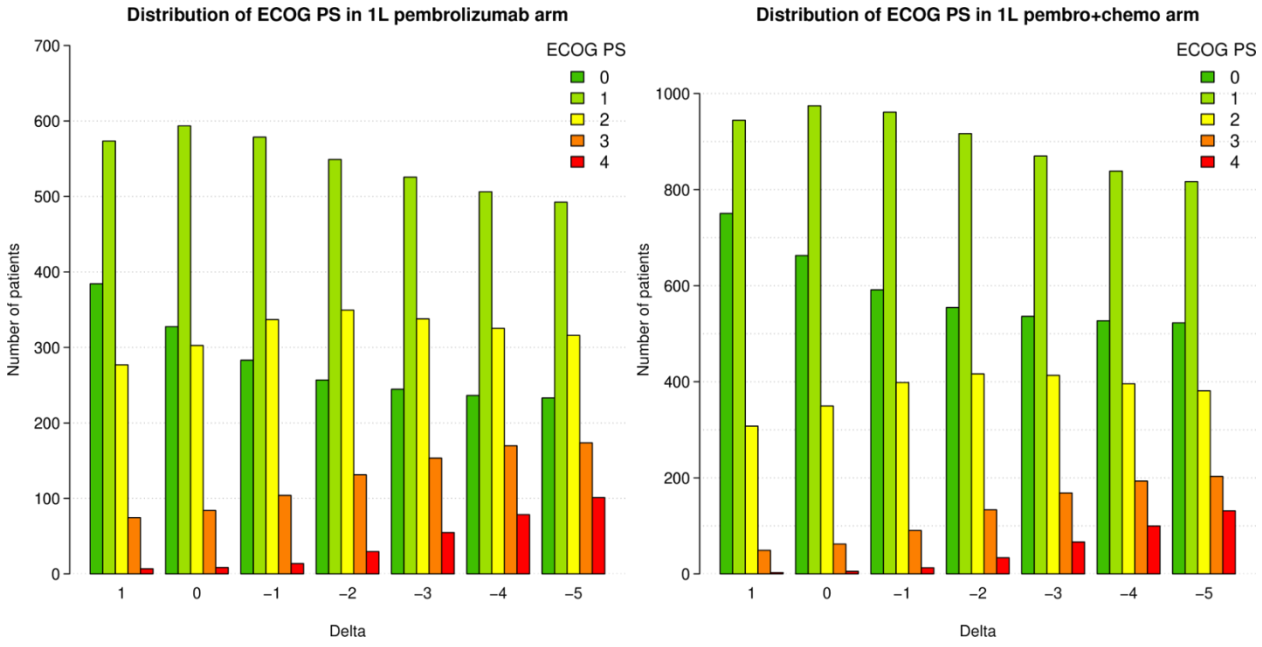


Figure 17 shows that negative values for δ shifted hazard ratios progressively in the direction towards the null and median survival times for the comparator arms to longer times, until achieving a plateau at δ=-3. Also shown in Figure 17, no tipping points could be identified for untreated pembrolizumab monotherapy or untreated pembrolizumab + pemetrexed + chemotherapy, indicating that our results are robust to deviations from random missingness for baseline ECOG PS. Furthermore, our results were robust in general to missingness assumptions for measured baseline covariates as shown with δ=0 under standard multiple imputation compared to the main analyses.

Figure 17: Tipping point analysis for missing baseline ECOG PS. Delta (δ) values of +1, 0, -1, -2, -3 and -4 corresponded to the observed mean ECOG PS shifts shown below of -0.35, +0, +0.44, +0.89, +1.30 and +1.61. MST represents the median survival time in months for the comparator to pralsetinib, either

pembrolizumab monotherapy or pembrolizumab + pemetrexed + chemotherapy. MST for pralsetinib was not estimable.

[redacted]

Quantitative bias analysis for unmeasured confounding

This analysis examines the effect of unmeasured confounding that would be required to nullify or reverse the conclusions of this study. We assume for interpretability that a hypothetical binary confounder U underlies the residual and/or unmeasured confounding on the estimated treatment effects from this study. By assessing how strong of a confounder U would have to be to nullify or reverse our conclusions, we can measure the robustness of this study. To do this, we calculate the bias B resulting from U as a function of

1. association of U with the outcome on the risk ratio scale (RRUD), and
2. imbalance of U between treatment arms on the risk ratio scale (RREU) as in VanderWeele et al. (2017). (33)

Because only risk ratios are handled, hazard ratios were converted to approximate risk ratios using the square-root transformation from VanderWeele (2017). (34) HRs from multiple imputation reported in Table 1 were used here for the bias plots for the worst-case scenario.

In Figure 18 and Figure 19, we plot bias curves for untreated pralsetinib versus pembrolizumab monotherapy and untreated pralsetinib vs pembrolizumab + pemetrexed + chemotherapy comparisons. For example, the black curve at the point estimate of [redacted] (adjusted risk ratio [redacted]) in Figure 18 plots the range of values for the association of U with survival and treatment assignment that would be needed to nullify our conclusions, i.e., that the unconfounded effect estimate adjusted for U would equal 1 on the risk ratio scale for pralsetinib vs pembrolizumab monotherapy comparison.

To assess the plausibility of unmeasured confounding, we also plot the observed associations of measured confounders with survival and treatment assignment from

this study along with 95% CIs. The bias plot shows that on the continuum of uncertainty in our results due to residual/unmeasured confounding, we expect that our results are robust when considering that important well-measured potential baseline confounders such as age and smoking history were neither highly prognostic of survival nor (except smoking history) highly imbalanced between treatment groups.

Figure 18: Bias plot for unmeasured confounding for untreated pembrolizumab monotherapy comparison ([redacted]). This graph plots unconfounded treatment effect estimates as risk ratios (ARR; adjusted risk ratio) after adjusting for a hypothetical unmeasured binary confounder over a range of confounder-exposure and confounder-outcome associations on the risk ratio scale. The colours map the strength of an unmeasured confounder (x and y axes) to the robustness of this study's conclusions (colour gradient). The worst-case strengths of measured baseline confounders are shown.

Figure 19: Bias plot for unmeasured confounding for 1L pembrolizumab comparison ([redacted]). This graph plots unconfounded treatment effect estimates as risk ratios (ARR; adjusted risk ratio) after adjusting for a hypothetical unmeasured binary confounder over a range of confounder-exposure and confounder-outcome associations on the risk ratio scale. The colours map the strength of an unmeasured confounder (x and y axes) to the robustness of this study's conclusions (colour gradient). The worst-case strengths of measured baseline confounders are shown.

Appendix 5: Updated mapping analysis

Summary of previous evidence and discussions

A summary of the previous evidence and discussions on health state utility values thus far:

- In the company submission (Section B.3.4.3, Table 56, pages 152-153) the health state utility values used in the untreated population (PF: 0.794; PD: 0.678) are higher than the pre-treated population (PF: 0.713, PD: 0.628).
- In clarification question C8 (page 66-68), the ERG queried this relationship and the company response explained that as patients progress and disease worsens, patients are expected to demonstrate deteriorating HRQoL. This is in line with health state utilities observed in previous NICE appraisals.
- Further, in the company response to clarification question C9 (pages 68-72) an update on the company mapping analysis was provided. This calculated comparable health state utility values in the untreated ([redacted]) and pre-treated ([redacted]) populations. Limited inference should be taken from the PD values given the small number of observations used to estimate these. Given the health state utility values are above general population norms, a conservative approach was taken to use the lower health state utility values from previous appraisals in the company base case as per the company submission.
- In key issue 11 (ERG Report, Section 4.2.8, bullet point 2, page 97), the ERG note that there is an inconsistency between the company's response to clarification question C8 and the updated mapping analysis provided in C9. Namely, the health state utility values used from previous appraisals showed a difference between untreated and pre-treated populations whilst those presented in the mapping analysis did not. Therefore, the ERG expressed concern regarding the validity of the utility scores used in the company base-case, not coming from the same source.

[redacted]

[redacted] An updated and corrected mapping analysis for utility scores is provided in the following section.

[redacted] This mapping analysis should supersede the previous mapping analysis provided in response to clarification question C9.

Updated mapping analysis

xxxxxx33 displays the number of patients and observations used for the updated mapping analysis.

[redacted]

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

[redacted]

Table 34 displays the health state utility scores from the updated mapping analysis. A random intercept liner mixed effects model was used with all post-baseline measurements as the response variable and with baseline utility as the only covariate.

Table 34: Results from updated utility mapping analysis (update of clarification response C9, Table 35, page 69)

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

[redacted]

xxxxxxx20-xxxxxxx23 displays the histograms and scatterplots for the untreated and pre-treated populations respectively.

20 [redacted]

21 [redacted]

22 [redacted]

23 [redacted]

Relationship between untreated and pre-treated populations

For PF health state utility values, the health state utility values estimated in the untreated population ([redacted]) are higher than those estimated in the pre-treated population ([redacted]) by [redacted]. This compares to a difference of 0.081 (0.794-0.713) between the untreated and pre-treated health state utility values used in the company submission.

For PD health state utility values, the health state utility values estimated in the untreated population ([redacted]) are higher than those estimated in the pre-treated population ([redacted]) by [redacted]. This compares to a difference of 0.050 (0.678-0.628)

between the untreated and pre-treated health state utility values used in the company submission. However, limited inference should be taken from the PD values given the small number of observations used to estimate these.

The relationship between the health state utility values from the untreated and pre-treated populations in the updated mapping analysis is now more in line with the argument presented in the response to clarification question C8. Although the magnitude is not as large as the health state utility values from previous appraisals, the health state utilities are lower in the pre-treated population compared to the untreated population. Roche hope that this updated analysis may allay some of the ERG's concerns presented in key issue 11 (ERG Report, Section 4.2.8, bullet point 2, page 97).

Scenario analysis using updated mapping analysis

As in the previous mapping analysis provided, health state utilities provided are above general population norms and therefore a conservative approach is taken not to use these utilities in the company base case and to stick with published health state utility values from previous appraisals. To explore the impact of this assumption on results, a scenario analysis is conducted assuming health state utility values from the updated mapping analysis were used in the economic model (Table 35). For both the untreated and pre-treated populations, scenarios were run using the updated mapping analysis for both PF/PD and just PF health state utility values. In all cases, ICERs are lower than the base case ICERs when the updated mapping analysis is used.

Table 35: Untreated and pre-treated scenario analysis with updated mapping analysis

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pralsetinib for RET fusion-positive advanced non-small cell lung cancer ID3875

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 6 December**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating RET fusion-positive advanced non-small cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Sanjay Popat
2. Name of organisation	Royal Marsden Hospital
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with RET fusion-positive advanced non-small cell lung cancer? ☒ A specialist in the clinical evidence base for RET fusion-positive advanced non-small cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Clinical expert statement

8. What is the main aim of treatment for RET fusion-positive advanced non-small cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To cause tumour response, to delay progression, and to improve overall survival, with an acceptable toxicity profile
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A response rate of over 50% would be considered clinically significant and meaningful
10. In your view, is there an unmet need for patients and healthcare professionals in RET fusion-positive advanced non-small cell lung cancer?	Yes, this is a group of predominantly young never smoking patients with an otherwise lethal malignancy for which there are no NHS funded RET-targeted therapies. RET positive NSCLC is not particularly sensitive to immunotherapy and so survival remains dismal
11. How is RET fusion-positive advanced non-small cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	RET patient identification is gradually coming on line with implementation of the NHS Cancer Test directory which funds RET testing, within the GLH Network infrastructure. 1st line: patients are generally treated with carboplatin-pemetrexed with/without pembrolizumab. Pembrolizumab or atezolizumab monotherapy is particularly ineffective with several datasets demonstrating that the surrogate of RET+ NSCLC (never-smoking NSCLC) our comes from pembrolizumab monotherapy trials vs chemotherapy and several real-world evidence datasets demonstrated poorer survival for immune-monotherapy than chemotherapy. The role of additional pembrolizumab to carbo-platin-pemetrexed is unknown. Hence carboplatin-pemetrexed is often used. Later lines: immune-monotherapy is particularly ineffective as demonstrated by several molecular registries of RET+ NSCLC and the outcomes of the surrogate of EGFR and ALK+ NSCLC in trials of docetaxel vs immune-monotherapy. Hence, patients are treated with docetaxel +/- nintedanib

	The vast majority of clinicians now follow the above paradigms although there will be some that are unfamiliar with these datasets. The current ESMO clinical practice guidelines for NSCLC were updated prior to the EMA license for pralsetinib allowing 1st line therapy, and hence currently only support RET inhibitors in the relapsed NSCLC setting. Impact: if approved within the EMA and proposed MHRA license, pralsetinib would be used as the preferred first line option for RET+ NSCLC, or if the patient has started treatment with chemo-immunotherapy prior to RET result available [RET result can take significant time to return], then when clinically appropriate. Hence, I agree with the BTOG expert colleague that "The technology would be an additional line of therapy, giving patients more options, and more lines of treatment."
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	I agree with my BTOG expert colleague: "No. Pralsetinib is an oral anti-cancer therapy whereas all other treatments are intravenous (IV). Pralsetinib would not require chemotherapy unit time or space. The treatment intent (palliative) remains unchanged." The drug would be used in the out patient setting No additional investment is required for delivery of pralsetinib, and RET testing is already commissioned.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	Yes, and I concur with my BTOG expert colleague: "The most recent data from the ARROW trial, an update presented at the ASCO Annual Congress in 2021(Curigliano et al., J Clin Oncol 39(15S) :9089-9089), showed the following:

• Do you expect the technology to increase health-related quality of life more than current care?	In RET+ patients who were treatment naïve, the Response Rate (RR) to Pralsetinib was 72%, Disease Control Rate (DCR) was 93%, and median Progression Free Survival was 13.0 months. Although this was not a head-to-head study, cross-trial comparison with what in the UK is likely to be the standard of care (Pembrolizumab, Pemetrexed, Carboplatin: KEYNOTE-189 trial) show a response rate of 47.6%, DCR = 84.6% and median PFS = 9.0 months (Rodriguez-Abreu et al., ASCO Annual Congress 2020). Consequently in these measures, Pralsetinib is superior to current Standard of Care. When used in the 2nd line (relapsed) setting, Pralsetinib demonstrated RR = 62%, DCR = 91% and median PFS = 16.5 months. This time the comparator would adenocarcinoma patients who received Docetaxel and Nintedanib in the LUME-Lung-1 trial (Reck et al., Lancet Oncology 2014). Here, the RR = 4.7%, DCR = 54% and median PFS = 3.4 months. Again, Pralsetinib is superior to the current standard of care." Increase in health related quality of life: Yes, I agree with the BTOG expert colleague that "the magnitude of median PFS benefit over standard of care is such that it is likely to lead to an Overall Survival benefit in the real world setting." I also agree with my BTOG expert colleague that in the currently enrolling first line trial of pralsetinib vs chemotherapy+/- immunotherapy: "if Pralsetinib is increasing survival, this may not be shown in AcceleRET because the primary end-point is median PFS, and cross-over from chemotherapy to Pralsetinib in event of progression is permitted within the trial design."
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I agree with my BTOG expert colleague that "Pralsetinib (with respect to this Appraisal) is only suitable for patients with advanced lung cancer and a proven RET-fusion."

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	I agree with my BTOG expert colleague that "From the healthcare professional perspective, Pralsetinib, which is oral, will be easier to use the current standard of care, which are intra-venous. There is less demand on chemotherapy units, and associated services. No additional requirements are needed in order to provide Pralsetinib, with lung oncology services being very familiar with oral anti-cancer drugs. From the patient perspective, the drug will be easier to take (fewer side effects, oral) and more convenient (long treatment cycles, no need for day-case attendance for treatment)."
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I agree with my BTOG expert colleague that "Treatment would continue so long as there is clinical benefit (as assessed by radiological response and symptomatic benefit), or until unacceptable toxicity develops."
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I agree with my BTOG expert colleague: "No"
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I agree with my BTOG expert colleague: "Yes, This is a novel, RET-specific targeted drug, and as such is innovative." I would suggest it and selpercatinib (the other RET inhibitor under NICE evaluation) are both step-changes in the management of the condition, and hence agree with my BTOG expert colleague that "Both Pralsetinib and Selpercatinib are step-changes in the management of RET+ lung cancer." However, only pralsetinib has a license for the treatment naive setting and hence, must be considered a unique "step change" in this setting.

	Unmet need: Yes, RET-positive NSCLC is a rapidly fatal cancer with no current targeted treatments NHS funded.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse events have been presented as per the ARROW trial data and as per the manufacturer's submission. These are proudly within what we currently observe for TKIs and are substantially improved compared to chemotherapy and immunotherapy. Indeed, at a time when COVID is endemic, new variants are emerging, immunity is waning, and Society guidelines recommend minimal hospital attendances, oral outpatient-based therapy makes most clinical sense.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I agree with my BTOG colleague that "Yes. Beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice." I agree with my colleague on all other answers in this section
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world data on immunotherapy monotherapy utility in relapsed RET+ NSCLC demonstrate a marked lack of efficacy for immunotherapy (doi: 10.1093/annonc/mdz167). Real world outcomes of immune-monotherapy first line in NSCLC demonstrate poorer survival (Peters et al. ESMO Virtual Plenary 8-9 April 2021)
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this	No

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1. The appraisal population is restricted to those with non-squamous NSCLC cell lung cancer which limits generalisability to patients with squamous NSCLC	This is reasonable as the numbers of squamous NSCLC that are RET positive is negligible. However, the utilities are likely to be similar and the final NICE recommendation should encompass all RET+ NSCLC given the negligible rates of squamous RET+ NSCLC, as clinicians will be faced with these patientsas RET testing becomes wider adopted.
Key issue 2. Exclusion of potentially relevant comparators listed in the NICE scope	Agree. For treatment-naïve patients chemo-immunotherapy is not evidence based for this group of patients and currently carbolatin-pemetrexed should remain the fundamental comparator. For relapsed patients I agree in excluding immunotherapy, as this is generally inert from real world evidence and trial data on the surrogate of EGFR/ALK+ NSCLC. For treatment naïve patients BSC is an unlikely comparator as these are young never smoker otherwise healthy patients, in general.
Key issue 3. Questionable generalisability to UK population	I personally think it unlikely there will be any major differences between ARROW and UK population. RET+ patients behave similar regardless of ethnic differences. Pralsetinib access will be the most significant impact to their survival, and not any UK-specific other healthcare issues
Key issue 4. Methodological problems with systematic literature reviews	The systematic literature review has been done to an expected standard. These reviews always have heterogeneity in the way outcomes are measured and reported, but outcomes are broadly similar
Key issue 5. Lack of comparative safety data	ARROW is a single-arm trial due to the rarity of RET+ NSCLC. A randomized trial is recruiting but it is not yet clear if this will continue to recruit to completion given challenges in recruitment and retention due to COVID. Hence, indirect comparisons for safety must be explored. I note that safety has been explored thoroughly by EMA who granted pralsetinib approval for first and subsequent lines on the basis of a beneficial efficacy:safety profile.
Key issue 6. Propensity score weighting analysis could have been conducted for comparison with platinum-based	No comment

Clinical expert statement

chemotherapy +/- pemetrexed	
Key issue 7. No correction for crossing curves in probabilistic sensitivity analysis	The issue seems resolved according to ERG
Key issue 8. Constant benefit of pralsetinib assumed without justification and based on immature data	No comment
Key issue 9. Substantial uncertainty in survival curve extrapolations due to immaturity of data	No comment
Key issue 10. Adverse event incidences included in the model potentially subject to error	No comment
Key issue 11. Lack of direct evidence to inform health-related quality of life	I think the company approach is reasonable; RET+ patients behave similarly to other advanced NSCLC patients

Are there any important issues that have been missed in ERG report?	Not to my knowledge.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Pralsetinib for treatment naïve RET positive NSCLC is a step-change treatment

Pralsetinib for relapsed NSCLC naïve RET positive NSCLC is a step-change treatment

RET-directed oral outpatient-based treatment is far more acceptable to patients than chemotherapy

RET-directed oral outpatient-based treatment has a different and likely less deleterious toxicity profile than chemotherapy

The AccelRET first line trial will not be able to determine a survival benefit for pralsetinib due to inbuilt crossover design

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Technical engagement response form

Pralsetinib for RET fusion-positive advanced non-small cell lung cancer [ID3875]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Technical engagement response form

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Eli Lilly and Company Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1. The appraisal population is restricted to those with non-squamous NSCLC cell lung cancer which limits generalisability to patients with squamous NSCLC	No	None
Key issue 2. Exclusion of potentially relevant comparators listed in the NICE scope	No	For the pre-treated population Eli Lilly believe the appropriate comparators are docetaxel and docetaxel plus nintedanib only. These were recently concluded as the most relevant comparators for this target patient population in the Final Appraisal Document for selpercatinib for RET fusion-positive advanced non-small-cell lung cancer.[1] *RET* fusion-positive patients are predominantly of non-squamous histology.[2] NICE recommends a number of therapy options for patients without genetic markers presenting with first line (untreated), advanced, non-squamous NSCLC. For patients who do not express any genetic markers nor tumour protein markers (e.g. PD-L1) in the first line setting, NICE recommends treatment with pembrolizumab combination therapy (TA683).[3] A market share study performed by Eli Lilly and

		Company for all non-squamous NSCLC, which included drugs for other genetic markers, found that pembrolizumab combination therapy had a market share of [redacted] in Q3 2019, giving it one of the highest market share of therapies recommended for cancers expressing no genetic or protein markers.[4] It is our assertion that pembrolizumab combination therapy market share has likely grown since these data were collected and it is now positioned as the most commonly used treatment for patients without a treatable mutation and remains the immunotherapy treatment of choice at first-line which makes up around 70-90% of treatment shares at first line.[1] **Figure 1. Market share data for first line treatment regimen in non-squamous NSCLC in the UK**  *May include targeted therapies **Notes 1**: [redacted] **Notes 2**: [redacted] **Source**: Eli Lilly and Company Ltd. Data on File. **References** 1. NICE [2021] Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer. Final Appraisal Determination. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10618. 2. O'Leary C, Xu W, Pavlakis N, et al. Rearranged During Transfection Fusions in Non-Small Cell Lung Cancer. Cancers (Basel) 2019;11 3. NICE [2021] Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta683 4. Eli Lilly and Company. Data on file. Share tracking NSCLC, 2019.
Key issue 3. Questionable generalisability to UK population	No	None
Key issue 4. Methodological problems with systematic literature reviews	No	None

Key issue 5. Lack of comparative safety data	No	None
Key issue 6. Propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed	No	Eli Lilly believe a comparison to platinum-based chemotherapy +/- pemetrexed is not relevant (see response to Key Issue 2). However, it is reasonable to request a population-adjusted indirect comparison based on aggregated data from the trial for docetaxel plus nintedanib (LUME-Lung 1) based on the methods described in Technical Support Document 18. Naïve estimates are likely to underestimate the effectiveness of this combination as RET-fusion positive patients are a different demographic compared to the broader NSCLC population which was concluded in the Final Appraisal Document for selpercatinib for RET fusion-positive advanced non-small-cell lung cancer.[1] Patients exhibiting *RET* fusion-positive NSCLC share many clinical features with those patients who have tumours driven by other oncogenic mutations, such as ALK, ROS-1 and EGFR.[2] Patients with *RET* fusion-positive NSCLC are typically of a younger age (≤60 years) with minimal or no prior history of smoking.[2] Data from a retrospective real-world registry study (IMMUNOTARGET registry, including patients from Europe, the US, Israel and Australia), found that 66.7% of patients with *RET* fusion-positive tumours had never smoked (compared with 6.7% who were current smokers) and that the median patient age was 54.5 years (range: 29–71).[2,3] Younger age and non-smoking status attributed to RET-fusion positive patients are expected to have a prognostic impact leading to better survival outcomes for a RET-fusion positive population from LUME-Lung 1 compared to the ITT population.[1] **References** 5. NICE [2021] Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer. Final Appraisal Determination. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10618. 6. O'Leary C, Xu W, Pavlakis N, et al. Rearranged During Transfection Fusions in Non-Small Cell Lung Cancer. Cancers (Basel) 2019;11 7. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321-1328

Key issue 7. No correction for crossing curves in probabilistic sensitivity analysis	No	None
Key issue 8. Constant benefit of pralsetinib assumed without justification and based on immature data	No	Eli Lilly do not agree with the ERGs assertion to apply a treatment waning effect to its base case to compensate for immature survival data. When presented with incomplete survival data, validation to external datasets and expert clinical judgement (Technical Support Document 14) should be undertaken when survival is immature and substantial extrapolation is required (particularly with OS in this case). Validation to landmark survival estimates from expert clinical opinion to choose the most reasonable survival curves is an appropriate method to validate survival projections. The application of a treatment waning effect in the base case disregards expert clinical testimony and is an extremely conservative assumption on the long-term treatment effect of the intervention. Although we agree there is substantial uncertainty over the long-term trajectory of OS, we believe this uncertainty could be more appropriately handled by exploring the impact of alternative survival curve choices for the intervention and comparator arms.
Key issue 9. Substantial uncertainty in survival curve extrapolations due to immaturity of data	No	Please see response to Key Issue 8 – Guidance in Technical Support Document 14 should be followed in the absence of longer survival follow-up and unreliability of interval validation methods. External validation to clinical datasets and to landmark survival estimates from expert clinical judgement are the most appropriate methods to validate survival extrapolations in this case.
Key issue 10. Adverse event incidences included in the model potentially subject to error	No	None
Key issue 11. Lack of direct evidence to inform health-related quality of life	No	None

Are there any important issues that have been missed in ERG report?	No	None

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Technical engagement response form

Pralsetinib for RET fusion-positive advanced non-small cell lung cancer [ID3875]

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If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

Technical engagement response form

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 6 December**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roche Products Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	--

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses ?	Response	ERG comment
Key issue 1. The appraisal population is restricted to those with non-squamous NSCLC cell lung cancer which limits generalisability to patients with squamous NSCLC	No	The marketing authorisation for pralsetinib does not differentiate between patients with squamous and non-squamous advanced non-small cell lung cancer (NSCLC). The company acknowledges that the population of rearranged during transfection (*RET)* fusion- positive squamous NSCLC patients is rare. The small proportion of squamous *RET* fusion-positive NSCLC patients enrolled in ARROW (1.4%) is expected to be reflective of what would be observed in United Kingdom (UK) clinical practice. European Medicines Agency (EMA) regulatory authorities considered that results were generalisable enough from non-squamous to squamous patients to grant a licence in the squamous indication. Due to the unmet medical need in all *RET* fusion-positive patients in the UK, it is crucial that all *RET* fusion-positive advanced NSCLC patients (non-squamous and	The ERG acknowledges that the proportion of squamous *RET* fusion-positive NSCLC patients enrolled in ARROW may reflect what would be observed in UK clinical practice. We reiterate that the appraisal population differs from the population described in the NICE scope. The appraisal population is restricted to non-squamous non-small cell lung cancer (NSCLC), whereas the population defined in the final National Institute for Health and Care Excellence (NICE) scope includes all patients with NSCLC.

		squamous histologies) have a *RET* inhibitor available as a treatment option in line with the proposed licensed indication. The selpercatinib appraisal consultation document (ID3743, Section 3.5, page 8) states that the company clinical expert expected there to be some level of response in squamous patients.(1) In addition it is also mentioned that the Cancer Drugs Fund (CDF) clinical lead said that the National Health Service (NHS) would follow the same recommendation in treatment for squamous NSCLC as for patients with non-squamous NSCLC and therefore, the committee agreed that the technology appraisal would apply to both squamous and non-squamous advanced NSCLC. Given the similar nature of the squamous issues across the two appraisals, the precedent set by ID3743 is adequate to cover the appraisal for pralsetinib and that the relevant population for this appraisal should be the full licenced indication including squamous patients.	With respect to the comments regarding decisions made by the European Medicine's Agency (EMA), the ERG has made an independent appraisal. With respect to the comments regarding the selpercatinib appraisal, the ERG notes that while the selpercatinib appraisal may share similarities with this one, that each appraisal must be taken on its own merits, so appeal to the selpercatinib appraisal cannot be assumed to have direct relevance to this one. It appears to be the case that very few RET positive patients will have squamous disease and that the percentage who do might be similar to that in the ARROW trial. Nevertheless, the indirect comparisons with pembrolizumab and pembrolizumab + pemetrexed + chemotherapy, comparators for squamous histology, used only non-squamous patient data from the Flatiron study. Therefore, the most appropriate populations would seem to be those with non-squamous histology.
Key issue 2. Exclusion of potentially relevant comparators	No	Treatment comparators for this appraisal should reflect the current standard of care for *RET* fusion-positive patients in the NICE treatment pathway.	The ERG acknowledges the comments made by the company and reiterates that the comparators chosen are not in line with the final NICE scope. This leaves some

<table>
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<td>listed in the NICE scope</td>
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<u>Untreated: Chemotherapy in combination with a platinum drug +/- pemetrexed treatment</u>

Roche acknowledges that both the clinical expert in the Evidence Review Group (ERG) report and the response from British Thoracic Oncology Group (BTOG) suggest that chemotherapy in combination with a platinum-based chemotherapy +/- pemetrexed treatment should be included as a comparator. We note the BTOG response states that patients "would follow NICE guidelines" (Section 9, page 4 (296)). We agree that for wild-type (WT) advanced NSCLC, chemotherapy in combination with a platinum-based chemotherapy +/- pemetrexed treatment would represent standard of care.

However, it is key that the comparator population in this appraisal are patients with (detected or undetected) RET fusion-positive advanced NSCLC. In a retrospective analysis examining the characteristics of patients with RET fusion-positive NSCLC in real-world practice in the United States, 46 patients were identified as RET fusion-positive out of a sample size of 5807.(2) Table 3 below provides an illustration of the clinical characteristics of RET+ and RET- cohorts. These patients demonstrate differing characteristics to WT NSCLC patients. RET fusion-positive patients tend to be younger, have never smoked and are more likely to have Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0-1 compared to WT NSCLC patients. These characteristics can be considered key differentiators in choice of treatment.

Table 3: Clinical characteristics of RET+ and RET- cohorts
<table>
<tr><th>Characteristics</th><th>RET+ (n=46)</th><th>RET - (n=5761)</th><th>RET+ vs RET- P</th></tr>
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questions regarding the relative effects of pralsetinib unanswered.

The rationale provided by the company to use comparisons that deviate from the final NICE scope rely heavily on expert opinion. Expert opinion is an important source of information, and the ERG believes that it is more reliable with support from rigorous quantitative data.

With respect to selpercatinib, the ERG reiterates that while the selpercatinib appraisal may share a number of similarities with this one, that each appraisal must be taken on its own merits, so appeal to the selpercatinib cannot be assumed to have direct relevance to this one.

The ERG is confused by the company's statement "comparator population in this appraisal are patients with (detected or undetected) RET fusion-positive advanced NSCLC". The final NICE scope cites a single population and specifies comparator interventions.

With respect to the comments regarding the unsuitability of best supportive care as a relevant comparator, the ERG acknowledges the company's assumption ("it is assumed BSC alone is not an established treatment
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					value*		option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate or are willing to have pharmacological intervention will be eligible for pralsetinib, hence, BSC is not an appropriate comparator for this appraisal"). The ERG has not seen any evidence to support this assumption. The ERG reiterates that best supportive care is included in the final NICE scope as a required comparator but not in the company's submission.
			Age, years (mean, Sd)	62.9 (11.0)	67.2 (10.2)	0.004	
			Stage IV at initial diagnosis, n (%)	34 (73.9)	3680 (65.2)	n/a	
			Histology, n (%) non-squamous squamous missing/unknown	45 (100.0) 0 (0.0) 1	4392 (79.4) 1138 (20.6) 231	<0.0001	
			Smoking history smoking history no smoking history	17 (37.0) 29 (63.0)	4703 (81.9) 1042 (18.1)	<0.0001	

		ECOG performance score, n (%) 0 1 2 3+ missing/unknown	 19 (61.3) 9 (29.0) 2 (6.5) 1 (3.2) 15	 1419 (33.6) 2079 (49.2) 593 (14.0) 135 (3.2) 1535	 0.02	

Platinum-based chemotherapy was not included as a comparator based on the following evidence:

- Roche conducted an advisory board with six leading UK NSCLC clinical experts in order to determine standard of care for *RET* fusion-positive patients. Clinical experts were asked what was considered standard of care for *RET* fusion positive patients or WT patients who demonstrated representative characteristics of *RET* fusion patients. Clinical experts stated that ECOG PS was a key determinant in the treatment decision. Patients with higher ECOG PS were more likely to receive platinum-based chemotherapy regimens. Therefore, given the better ECOG PS status among *RET* fusion positive patients, it was recommended platinum-

		based chemotherapy regimens should not be considered standard of care. ● Similar feedback was received in a recent qualitative questionnaire with clinicians in lung cancer which indicated that a key motivation for prescribing chemotherapy regimens in the first-line setting is that this is for patients who are not able to tolerate pembrolizumab + pemetrexed + chemotherapy (i.e. worse ECOG PS patients).(3) ● The appraisal company clinical expert has also commented that there is not a lot of use of platinum doublet chemotherapy in the *RET* fusion-positive first line untreated setting and therefore, advised the company to exclude this as a potentially relevant comparator in the untreated population. ● In the selpercatinib appraisal consultation document (TA10618, Section 3.2, page 5-6) the committee agreed that nearly all patients receive immunotherapy +/- chemotherapy combination in the first line setting, suggesting that pembrolizumab + pemetrexed + chemotherapy is the true standard of care for *RET* fusion-positive patients and any use of chemotherapy treatment alone would be negligible.(1) The committee therefore concluded that immunotherapy treatment should be removed as comparators from the second-line setting. *Untreated: other comparators excluded* The ERG report (Section 2.3) also states, based on clinical expert opinion that the following comparators are also missing: nivolumab plus ipilimumab, atezolizumab monotherapy and	

		atezolizumab plus bevacizumab plus carboplatin plus paclitaxel. Roche notes that these comparators all have licensed indications in this setting. However, comparators in the submission should represent the standard of care in a setting. The company submission (Table 1 and 2, page 13-16) outlines the non-squamous untreated and pre-treated comparators suggested by National Institute for Health and Care Excellence (NICE) in the final scope, with justification for their inclusion or exclusion. For these three treatments stated above, further justification is given below: ● Nivolumab with ipilimumab and chemotherapy (TA724) has not been recommended by NICE for use within its marketing authorisation ● In the professional submission by BTOG they did not advise that any of the above comparators should be considered standard of care the above comparators as first line treatments of choice. (BTOG Professional organisation submission, page 4-5) ● The appraisal company clinical expert mentioned that there is minimal usage of atezolizumab, bevacizumab, carboplatin plus paclitaxel in the relevant appraisal population *Untreated: comparators included* As per advice received in the advisory board, from the company clinical expert and following advice from the committee in the	

		selpercatinib appraisal, the untreated comparators in the updated company base case have remained unchanged: ● Pembrolizumab + pemetrexed + chemotherapy ● Pembrolizumab monotherapy. *Pre-treated comparators* The following comparators from the NICE scope have been excluded from the comparator list in this submission: ● Selpercatinib: ○ As stated in the selpercatinib company submission, the submission sought access via the CDF. Selpercatinib is now listed in the CDF for the pre-treated setting (2nd line) and is therefore not eligible to be a comparator in this setting. ● Atezolizumab monotherapy/ atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP)/ pembrolizumab monotherapy: ○ Patients are not eligible for any immunotherapy re-challenge regardless of line of therapy. As mentioned in the untreated comparators sections patients are expected to receive immunotherapy (combination or monotherapy) in the untreated setting and therefore, any immunotherapy agent	

		in the second line setting is not considered to be an eligible comparator. This is an identical approach to that taken and approved by the committee in the selpercatinib appraisal consultation document (Selpercatinib ACD, section 3.2, Page 6). The committee concluded that docetaxel and docetaxel with nintedanib were the appropriate comparators for pre-treated patients with *RET* fusion-positive NSCLC. Therefore, as per advice received in the advisory board, from the company clinical expert and following advice from the committee in the selpercatinib appraisal (ID3743), the untreated comparators in the updated company base case have remained unchanged: ● Docetaxel monotherapy ● Docetaxel + nintedanib ● Platinum-based chemotherapy +/- pemetrexed maintenance (in PD-L1 ≥50%) (which represents a combination of platinum doublet and pemetrexed with carboplatin, as per clinical expert advice from the advisory board) *Squamous* There was a very small number (1.3%, 2/233, total efficacy population) of squamous patients enrolled into the ARROW study and therefore a squamous subgroup analysis/indirect	

		treatment comparison is not considered feasible. As per the ERG report (page 31), there is mention that a NICE clinical expert noted the following: *"the company is making the assumption that RET fusions are so rare in S NSCLC that only the NS NSCLC pathway needs to be considered. From the TA point of view I think this is reasonable as it makes things simpler (NHSE will allow use of pralsetinib in patients with RET fusion S NSCLC in any case if the current indication is recommended)".* *<u>Best supportive care (BSC)</u>* Given the availability of other treatments, it is assumed BSC alone is not an established treatment option for patients who can tolerate, or are willing to have, pharmacological intervention. It is assumed that only patients who can tolerate, or are willing to have pharmacological intervention will be eligible for pralsetinib, hence, BSC is not an appropriate comparator for this appraisal. The selpercatinib ERG report (Section 2.5, Table 4, page 29) also recommended the exclusion of BSC as a comparator.	
Key issue 3. Questionable generalisability to UK population	No	ARROW is a Phase 1/2, multicentre, non-randomised, open-label, multi-cohort study, with the Phase 2 dose expansion phase conducted in 13 countries. UK clinical experts confirmed to Roche that the enrolled population is similar to other oncogenic driver clinical trials which have been used as evidence sources for UK health technology appraisal (HTA). (4, 5) Therefore, the study population can be considered generalisable to UK clinical practice and applicable for decision making.	The ERG acknowledges that clinical experts have confirmed to Roche that the population enrolled in the ARROW trial is similar to populations in other oncogenic driver clinical trials which have been used as evidence sources for UK technology appraisals. However, it is unclear what the value of the comparison with the LIBRETTO-001 study is in informing generalisability to UK clinical practice. With respect to the statement by

Table 4 below shows a side by side comparison of the baseline demographics for *RET* fusion positive NSCLC patients for both ARROW and LIBRETTO-001 studies. Both data sets are closely matched demonstrating that a typical *RET* fusion-positive patient is younger than an average WT NSCLC patient and they have better performance scores and tend to be non-smokers.

Table 4: Comparison of pralsetinib and selpercatinib baseline characteristics

Characteristics	Pralsetinib (ARROW) Measurable Disease Population n=216 (Company Submission, Table 8, page 43)	Selpercatinib (LIBRETTO-001) Total population n=253 (Company Submission, Table 9, page 52)
Median age, years (range)	60.0 (26-87)	61.0 (23-86)
Race, %		
White	52.3	51.4
Asian	38.4	40.7
Other	0.9	3.2

the BTOG, the ERG reiterates the value of empirical data to support expert opinion.

On this basis, the ERG believes that the extent to which the ARROW study population is representative of UK patients with respect to demographic and disease characteristics remains unclear.

		ECOG performance status, %		
		0	33.8	36.8
		1	63.4	61.3
		2	2.8	2.0
		Smoking history, %		
		Never	61.6	69.6
		Former	34.3	28.5
		Current	2.8	2.0
		Missing/Unknown	1.4	0
		The company also highlight the professional organisation submission provided by BTOG (Section 18, page 11), who stated the following when asked whether the clinical trial on the technology reflect current UK clinical practice: "*Yes, beyond the usual caveats of how well any clinical trial represents the Real World clinical experience, the trial data reflects current UK practice*".		

Key issue 4. Methodological problems with systematic literature reviews	No	The Systematic Literature Reviews (SLRs) submitted were performed in accordance with NICE guidelines and supported methods, and reported according to PRISMA guidelines.(6-9) Limitations associated with evidence generated were acknowledged in the submission but they are related with the lack of evidence available in the population under assessment and not with the methodologies used. All efforts were made to overcome the limitations identified. Despite the methodological issues pointed out by the ERG, with which the company disagrees, there is no evidence that relevant studies/evidence were missed. It should be noted the ERG has not presented additional suggestions. *RET-fusion positive NSCLC SLR (SLR 1)* • Search: The ERG note that trials registers were not searched and that the search facet for *RET* might have benefited from the inclusion of more synonyms (ERG report, Section 3.1.1, page 36-7). The search approach conducted took into consideration all core databases identified in NICE guideline, including Cochrane Central Register of Controlled Trials (CENTRAL).(6, 7) Regarding the search terms used to build the strategy, as mentioned in NICE guidelines, although it is important that searches for systematic reviews attempt to identify all the relevant literature, there needs to be a trade-off between sensitivity and precision, in a way to not compromise the feasibility of the study. The most important point is to run quality	The ERG acknowledges that the systematic literature reviews were reported in accordance with PRISMA guidelines. The ERG highlights the difference between reporting quality and methodological quality. The ERG's appraisal uses the report to assess the methodological quality. the ERG also notes that in a few places it doesn't seem that NICE guidance, or Cochrane methodology were adhered to (see below). The ERG acknowledges the company's statement that "there is no evidence that relevant studies/evidence were missed". The ERG's response to this statement is that the claim regarding no evidence cannot be interpreted as an adequate response to the ERG's comment that potential sources of relevant data, such as trials registers, were not searched, since evidence that no trials were missed would have to be generated by searching trials registers. Searching trials registers is recommended by Cochrane (see Chapter 4 of the Cochrane Handbook).

		checks in the search develop to ensure that relevant trials were not missed.(6-8) Although Roche acknowledge that further terms could have been used to describe *RET* population, efforts were made to check the quality and accuracy of the search strategy used, namely the verification of search strategies against literature available; run searches with and without certain search terms and assess the differences between the results obtained; check the bibliographies of included studies to ensure that all relevant papers have been retrieved by the search strategy used. For all mentioned, Roche believe that the searches conducted were explicitly and transparently shared and follow the guidelines and best practice. The search strategy does not compromise any conclusion that might come from the assessment of the SLR results and therefore should not be viewed as a barrier to access. Furthermore there is no evidence that important evidence has been missed. • Eligibility criteria: The ERG note eligible comparators for SLR 1 are not clear from the study eligibility information presented. Therefore, the nature of the treatment comparisons at this stage of the evidence synthesis is uncertain and it is unclear to what extent the selection of comparators reflects current practice in the UK NHS (ERG report, Section 3.1.2, page 41) The objective of the SLR was to assess the clinical evidence available for the treatment of patients with locally advanced or metastatic *RET*-fusion positive NSCLC and to allow a	With respect to the lack of clarity of the comparators chosen, the ERG acknowledges the company's statement that "Once there was no restriction in the eligibility criteria, the interventions used in the current practice in the UK NHS are naturally included in the list and there is no risk in missing important information regarding those interventions due to the eligibility criteria defined." The ERG's response to this statement is that the fact that all comparators may have been included

		comparison of pralsetinib with relevant comparators used in clinical practice. Considering the expected challenges in finding evidence in this population, no restrictions were defined for the intervention/comparators in the eligibility criteria. This allowed any study in the *RET*-fusion positive population to be considered for assessment regardless of the intervention used. The ERG states that "*it is unclear to what extent the selection of comparators reflects current practice in the UK NHS*". Once there was no restriction in the eligibility criteria, the interventions used in the current practice in the UK NHS are naturally included in the list and there is no risk in missing important information regarding those interventions due to the eligibility criteria defined. • Data Extraction: The ERG state the data extraction process for SLR 1 is not in line with recommended good practice i.e., dual, independent data extraction, particularly for outcome data. The ERG does not consider that the process described by the company would sufficiently address the risk of bias or error (ERG report, Section 3.1.3.2, page 44) According to the SLR methods supported by NICE (2), "*The number of researchers that will perform data extraction is likely to be influenced by constraints on time and resources, (...) as a minimum, one researcher should extract the data with a second researcher independently checking the data extraction forms for accuracy and detail. If disagreements occur between assessors, they should be resolved according to a predefined strategy using consensus and arbitration as appropriate*."	does not address the issue that the actual comparators included are not clearly specified. The ERG notes that this issue could be resolved by clarifying the comparators used in the actual analyses. The ERG acknowledges that the number of researchers that will perform data extraction is likely to be influenced by constraints on time and resources, (...) as a minimum, one researcher should extract the data with a second researcher independently checking the data extraction forms for accuracy and detail. If disagreements occur between assessors, they should be resolved according to a predefined strategy using consensus and arbitration as appropriate.") However, the reference to this citation (2. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. BMC Cancer. 2021;21(1):28.) seems mistaken.

		During the clarification questions phase, Roche shared in detail the process for data extraction in this review, that consisted of having one reviewer doing the initial extraction and a second reviewer confirming the extraction performed by: ○ Reviewing the publication(s) associated with the study for extraction, highlighting any relevant data for extraction ○ Checking that all data from the publication(s) had indeed been extracted into the DET in the correct cell (in this way, any data 'missed' by the first extractor was included in the Excel sheet – any additional data extracted were highlighted and checked by the first extractor [any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser]) ○ Checking that the correct values had been extracted (any disagreements between the two reviewers resolved by consensus or referred to the strategic adviser) Roche believe the process followed was compliant with NICE guidelines and should therefore not be the reason to question the robustness of the results presented. • Quality Assessment: The ERG state the rationale for excluding some studies from the methodological	The ERG is aware that NICE recommends that "title and abstract screening should be undertaken independently by 2 reviewers" (https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf). The ERG also notes that the Cochrane Handbook recommends independent dual extraction. The ERG acknowledges that the company conducted a feasibility assessment to exclude 30 of the 38 studies included in the SLR. The ERG's response is that without further details regarding the additional studies, the ERG cannot assess the feasibility assessment and comment on the legitimacy of excluding those studies. The

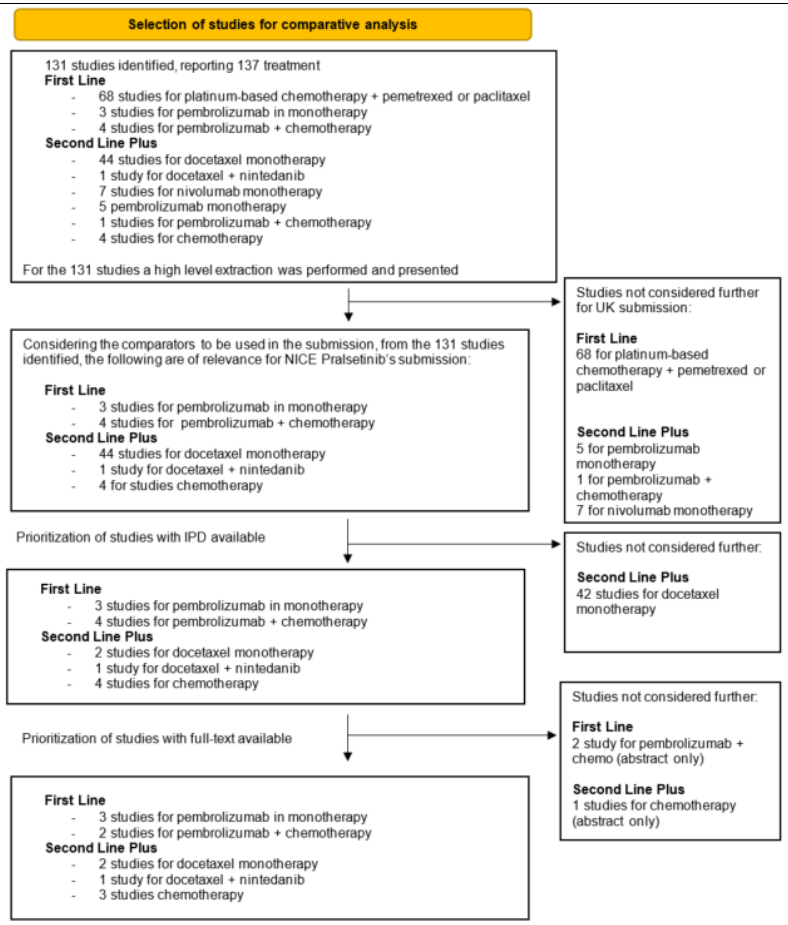
		assessment table (Table 10) was not explained (ERG report, Section 3.1.4.1, page 45) The main goal of the SLR was to identify the clinical evidence to support the indirect treatment comparisons of pralsetinib versus standard of case, and ultimately inform the cost-effectiveness analysis. Therefore, a feasibility assessment (FA) was conducted to identify which of the studies included in the SLR could be further assessed and be used to generate comparative evidence. For that reason, although 38 studies were included in the SLR only 8 were included in the indirect treatment comparisons (ITCs). The quality assessment is presented for the studies that passed the FA and were included in the ITCs, as this is the information used to inform the cost-effectiveness analysis. All the studies that were included in the SLR but excluded at the FA step were not extracted or assessed further and have no impact in the submission. *<u>WT NSCLC SLR (SLR 2)</u>* Considering the significant data gaps resulting from SLR 1, a complementary method was explored considering not only patients with *RET* fusion-positive NSCLC, but also WT patients. For that, a new and independent SLR with a new research question was designed and conducted. It is important to note that with this not being the main clinical SLR in the submission and considering the amount of evidence available for NSCLC WT in any treatment line, some prioritization exercises were needed to ensure the feasibility of the analysis without	ERG notes that this issue could be resolved by providing additional details about reasons for excluding the excluded studies. The ERG notes acknowledges that a different SLR to answer a different question is legitimate. The ERG acknowledges the company's statement that "some prioritization exercises were needed to ensure the feasibility of the analysis without compromising the quality of results obtained". The ERG's response is the feasibility exercises need to be made explicit in order to be appraised.

		compromising the quality of results obtained. Additionally, once different research questions and objectives were defined for the two SLRs, it is not inadequate that different methodologies (searches, eligibility criteria etc.) were used as well, especially considering that those (question and goal of a review) are the main drivers for the methodology definition. • Search Unlike the scenario of the first review in *RET*-fusion positive population, in the WT space there is a huge amount of data available, especially when considering all lines of treatment. As described in the SLR methods supported by NICE,(8) scoping searches may provide a good understanding of the evidence available for a certain scope, and researchers have the option of justifying a decision to limit study design based on the results obtained in such preliminary assessment. While in some cases there are evidence gaps clearly identified and a range of study designs may be needed to address the research questions, in others it becomes very obvious that the scope in question is quite populated. Additionally, according to NICE guidelines, "*Depending on the review question, it may be appropriate to limit searches to particular study designs. For example, for review questions on the effectiveness of interventions, it may be more efficient to search for systematic reviews, followed by controlled trials followed by observational studies. This prevents unnecessary searching and review work*."	The ERG also reiterates that there was neither a description of data extraction methods for SLR 2 nor tabulation of extracted, eligible studies. The figure below partly addresses this problem. Based on the company's explanation, and background evidence that randomised trials are (all things being equal) more methodologically sound than observational studies, the ERG acknowledges that the exclusion of non-randomised studies is unlikely to impact on the validity of the SLR results.

		Based on the knowledge in the space and the results of preliminary assessments showing a lot of evidence available for the WT NSCLC, and considering what is referred in the guidelines in terms of the studies designs to be considered, Roche believe that the prioritization of randomised control trials (RCTs) over other study designs does not compromises the findings of the SLR. Regarding the broadness of the search strategy used, as mentioned for SLR 1, although it is important that searches for systematic reviews attempt to identify all the relevant literature, there needs to be a trade-off between sensitivity and precision, in a way to not compromise the feasibility of the study. The most important point is to run quality checks in the search develop to ensure that relevant trials were not missed. Although Roche acknowledge that further terms could have been used to describe NSCLC, efforts were made to check the quality and accuracy of the search strategy used. • Eligibility criteria Considering that the goal of the SLR was to inform the cost effectiveness assessment, the outcomes used in the economic mode (PFS, OS) were used to prioritize the list of outcomes to be included. For endpoints related with safety please also consider the points raised in response to key issue 5, where it is shown that indirect comparison of safety endpoints is not feasible and the impact in the model is not significant. However, from the 14 studies excluded based on outcomes at full publication review, there were no studies that reported relevant clinical outcome data for treatment arms of interest (and so none	Regarding the broadness of the search strategy used, the ERG acknowledges the importance of quality checks. Nonetheless, the ERG's concerns that the search facet in SLR 1 for RET and the search facet in SLR 2 for NSCLC would have benefited from the inclusion of more synonyms remain. Regarding eligibility criteria, the ERG refers the company to the response below relating to Key Issue 5.

		of the studies could have been considered for inclusion in the analyses, even if further outcomes were considered in the eligibility criteria). Most of the publications excluded based on the "outcomes" were protocols or reported non-clinical/safety outcomes e.g. VEGF/MMP9 expression levels. • Study selection After running the searches and screening the records according to the eligibility criteria defined, the SLR included 131 studies to move forward for feasibility assessment. The process to select studies for comparative analysis is described in Figure 1. It is important to note that given the source of data for pralsetinib (single-arm study), limited comparative options are available. In this scenario the following option can be performed: o Propensity score analysis (adapting for important prognostic factors) when individual patient data (IPD) is available for both studies (pralsetinib and comparator) o Matching adjusted indirect comparison (MAIC) adjusting pralsetinib patients the comparator arm. This option adjusts away all population particularities of *RET*-fusion positive patients so is not considered appropriate for the intent goal o Naive comparisons where there are no population adjustments. In this case it is important that the population characteristics of the comparator's arm are as close to ARROW as possible.	The ERG acknowledges the limited number of comparative options, and the challenges associated with them. However, the ERG does not believe that the limited options and challenges preclude rigorous indirect treatment comparison for adverse events. Also, on page 69 of Document B of the company submission, the company states: "Propensity scoring is a recognised technique used in controlling for selection biases when combining multiple sources of non-randomised evidence."

		Considering the options available, and having in mind that no network analysis is possible, it seems appropriate to prioritize studies to which IPD is available. In addition, as results of different studies are not being connected, having more than one study per comparator does not bring additional value. For that reason one study per comparator was prioritized. **Figure 1: Selection of studies for comparative analysis**	



From the final list of studies, one of the studies for chemotherapy in 2L was reported in a Chinese paper. This was assessed based on title and abstract information but it was not

The ERG acknowledges the challenges with translating studies. The ERG believes that the information stated in the abstract gives

		translated for further inclusion. The ERG stated: "*The ERG is not convinced that sample size and/or ethnicity are appropriate reasons for exclusion (ethnicity is not listed as an exclusion criterion for SLR 2) and therefore it would have been preferable to have this paper translated and include the comparator data*" (ERG report, Section 3.1.2, page 43). The following issues indicate that the translation and inclusion of this publication would not have impacted the analyses presented: o The only arm relevant from this study is pemetrexed combined with platinum (n=55) - comparative analyses with pemetrexed followed by carboplatin (GOIRC 02-2006 + NVALT7: naïve comparison) and carboplatin or cisplatin plus pemetrexed (IMpower132: PSA) are already available and are based on larger sample sizes o Thus, although sample size was not a criterion for selection into the SLR/analyses, it is important to note that the study size is notably smaller than the studies included in the SLR/analyses and selected for comparative analyses; thus this study would not have been selected for comparative analyses o The comparative analyses focussed on OS/PFS but the Wang 2017 English abstract states that only short-term clinical effects are reported (follow-up time not explicitly reported), with the results stated as differences in PFS/OS between groups with no HRs presented – therefore, it is likely that the survival data	sufficient reason, at the very least, to make a final decision regarding inclusion after reading the full text. The ERG acknowledges that the sample size in this study is smaller than in some other studies. The ERG's response to this point is that sample size was not a stated exclusion criteria.

		are immature and presented in the format of OS/PFS rates at 1 year with no HR available On an additional note, the citation of this article was Wang C. et al. Comparison of docetaxel and pemetrexed combined with platinum in treatment of NSCLC after failure of gefitinib therapy. [Chinese]. 2017; 32(2):164-167, whereas the article cited on p.43 of the ERG report and cited as ref 22 was Wang J, Zhang S. [Targeted therapy for advanced non-small cell lung cancer in the elderly]. Chin J Lung Cancer 2009;12(7):821-5. The final list of studies considered appropriate for comparative analysis is outlined in the Company Clarification response (B25, Table 23, page 44). Study selection using sample sizes was applied only for docetaxel in the pre-treated setting. In this case, considering that POPLAR is a phase II study, compared to OAK which is phase III and therefore represents a more robust evidence base to perform the comparison. About the general process of study selection for the comparative analysis, the ERG "*questioned why only PDL-1 status, histology; pooled analyses; or studies with the largest sample size were the only criteria for matching with the ARROW study*". As it is possible to understand from the points mentioned above those were not the only points considered. Because those were the differentiating points they represent the rationale for exclusion for some of the studies, but all the characteristic of the studies and eligibility criteria of the SLR were considered. The company believes that the process allowed a transparent and unbiased assessment of the evidence available and there is	

		no evidence that important studies were missed or that other relevant data was not included. • Data extraction See corresponding section in SLR 1. • Quality assessment The assessment was conducted and is displayed in Appendix 1. However, it is important to mention that as only naive comparisons are performed with the data from those studies and only one arm of the study was considered, randomization is lost and most of the points in the quality assessment are not of relevance.	The ERG's concerns regarding the methodological quality of the SLRs remain.
Key issue 5. Lack of comparative safety data	Yes	As per the company response to clarification question 25 (d), ITCs of safety outcomes are not feasible. There are different mechanisms of action, different treatment durations, follow-up times and trial designs which make a comparison potentially misleading. Additionally, very limited data is available for the comparators studies with most of the adverse events being grouped (e.g. any adverse event, any treatment related adverse event), which does not allow the differentiation in the safety profiles of the different treatments. This is worsened by the fact that mainly naive comparison would have been possible with very few safety endpoints per comparator, and not allowing for proper adjustments. In light of the above limitations of comparative safety analyses, this is not an appropriate analysis to conduct in this setting.	The ERG acknowledges the company's statement that there is limited data for the comparator studies. Nonetheless, given that there is some data, the ERG reiterates the concern that comparative safety data should be provided.

		A descriptive safety analysis of pralsetinib compared to pembrolizumab + pemetrexed + chemotherapy in the untreated setting is provided in Appendix 2. *<u>Clinical expert opinion</u>* We note that in the statement from BTOG, no concerns were held regarding the safety profile of pralsetinib suggesting that it is likely to be favourable in comparison to current standard of care: "*Although formal, comparative, Quality of Life data has not been published, Pralsetinib has been to have a favourable side-effect profile. In ARROW, common grade 3 or worse treatment-related adverse events were neutropenia (18%), hypertension (11%), and anaemia (24 [10%). There were no treatment-related deaths in this population. Current chemotherapy / chemoimmunotherapy combinations have a worse side effect profile than this. The combination of greater efficacy, longer duration of activity, and more favourable profile is highly likely to result in improved Qualitty* [quality] *of Life compared to standard of care, for patients receiving Pralsetinib*. […] *From the patient perspective, the drug will be easier to take (fewer side effects)*" (BTOG Professional organisation submission, page 8). *<u>Impact on results</u>* In terms of cost-effectiveness, the impact of comparative safety data on results is negligible. For example, in the pralsetinib	The ERG notes that in the absence of more mature data, it is difficult to appraise the expert opinion of the BTOG. The ERG acknowledge the BTOG's statement that "*formal, comparative, Quality of Life data has not been published*".

		untreated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. The absence of comparative safety data should represent a substantial barrier to access. We note that in the selpercatinib appraisal (which also represented a single-arm study in *RET* fusion positive advanced NSCLC), no comparative safety data was provided and this was not viewed as a key concern either by ERG or committee. *Future evidence* The issue of comparative safety will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of *RET* fusion-positive, advanced NSCLC. Recruitment is expected to be completed in [redacted] with results expected in [redacted].	In terms of impact on results, in the absence of more mature data, the ERG cannot confirm the extent to which the lack of safety data impacts on results. The ERG was confused by the following statement "The absence of comparative safety data should represent a substantial barrier to access."
Key issue 6. Propensity score weighting analysis could have been conducted for comparison with platinum-based	Yes	*Untreated setting* As per the response to key issue 2, platinum-based chemotherapy +/- pemetrexed is not standard of care for *RET* fusion positive advanced NSCLC patients and therefore was not included as a comparator in the submission. Therefore, a comparison using the Flatiron EDM dataset is not seen as necessary. *Pre-treated setting*	With respect to the company's comments regarding the untreated setting, the ERG refers to our response to Key Issue 2 above. With respect to the company's comments regarding the pre-treated setting, the ERG acknowledges the imbalances in the populations. The ERG nonetheless believes that a propensity score weighting analysis could have been conducted for comparison with platinum-based chemotherapy +/- pemetrexed. Despite the remaining

chemotherapy +/- pemetrexed		As part of the initial submission, Roche investigated the feasibility of using the Flatiron EDM dataset to inform the platinum-based chemotherapy +/- pemetrexed arm of this comparison. The results of this comparison were provided in the Flatiron indirect treatment comparison technical report provided as part of the submission reference pack (EDM SCA Pralsetinib vs EDM cohorts for NSCLC, Appendix G, Section 9.7.3, pages 214-233). In the Flatiron EDM dataset, 177 (pre-adjustment) patients were identified as having received platinum-based chemotherapy +/- pemetrexed as second-line treatment. Table 5 shows that age and race are highly imbalanced, and smoking history and metastases-related variables are severely imbalanced. The remaining variables are all imbalanced to some extent as well. Note however that since metastases are underreported in the EDM, related variables are not used for adjustment and residual imbalances are not considered to be a crucial factor in determining the reliability of the analysis. **Table 5: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given platinum-based chemotherapy +/- pemetrexed in pre-treated setting**	imbalances it provides estimates that have to be regarded as valuable given the alternative of a naïve comparison. Other methods might also have been explored to respond to lack of overlap in covariates such as regression on the matched sample, as recommended in TSD 17.

	Level	Platinum-based chemotherapy	Pralsetinib	SMD
n		[redacted]	[redacted]	
Age (%)	< 65	[redacted]	[redacted]	0.627
	>= 65	[redacted]	[redacted]	
Sex (%)	F	[redacted]	[redacted]	0.205
	M	[redacted]	[redacted]	
Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	1.371
	No history of smoking	[redacted]	[redacted]	
ECOG (%)	0	[redacted]	[redacted]	0.067
	1	[redacted]	[redacted]	
Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.175
Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.342
	STAGE IV	[redacted]	[redacted]	
Race (%)	White	[redacted]	[redacted]	0.534
	Other	[redacted]	[redacted]	
	Unknown	[redacted]	[redacted]	
Sum of total metastases (median [IQR])		[redacted]	[redacted]	2.473
Metastases (%)	Isolated brain/CNS site	[redacted]	[redacted]	3.735

	None	[redacted]	[redacted]	
	Other	[redacted]	[redacted]	
Brain/CNS metastasis only (%)	0	[redacted]	[redacted]	0.803
	1	[redacted]	[redacted]	
Liver metastasis only (%)	0	[redacted]	[redacted]	0.494
	1	[redacted]	[redacted]	

Following weighting, Table 6 shows that only time from initial diagnosis is balanced among covariates used for adjustment (SMD<0.1). The remaining variables are at least moderately imbalanced. The imbalances are due to the low number of patients (177) in the platinum-based chemotherapy +/- pemetrexed arm relative to the number of population characteristics that are targeted to be balanced in conjunction with the existing differences in these variables at baseline. The imbalances between characteristics after weighting cast doubt on the validity of results and will likely lead to a bias in the hazard ratio and any other estimates resulting from this analysis.

Table 6: Baseline characteristics of the untreated ARROW trial participants given pralsetinib and Flatiron EDM cohort given platinum-based chemotherapy +/- pemetrexed in pre-treated setting with adjustment

	Level	Platinum-based chemotherapy	Pralsetinib	SMD	Adjusted
Age (%)	< 65	[redacted]	[redacted]	0.291	Y
	>= 65	[redacted]	[redacted]		
Sex (%)	F	[redacted]	[redacted]	0.17	Y
	M	[redacted]	[redacted]		

		Smoking history at baseline (%)	History of smoking	[redacted]	[redacted]	0.431	Y
			No history of smoking	[redacted]	[redacted]		
		ECOG (%)	0	[redacted]	[redacted]	0.128	Y
			1	[redacted]	[redacted]		
		Time from initial diagnosis to first dose (months) (median [IQR])		[redacted]	[redacted]	0.038	Y
		Stage at initial diagnosis (%)	STAGE I, II, or III	[redacted]	[redacted]	0.169	Y
			STAGE IV	[redacted]	[redacted]		
		Race (%)	White	[redacted]	[redacted]	0.178	Y
			Other	[redacted]	[redacted]		
			Unknown	[redacted]	[redacted]		
		Sum of total metastases (median [IQR])		[redacted]	[redacted]	2.403	N
		Metastases (%)	Isolated brain/CNS site	[redacted]	[redacted]	2.787	N
			None	[redacted]	[redacted]		
			Other	[redacted]	[redacted]		
		Brain/CNS metastasis only (%)	0	[redacted]	[redacted]	0.721	N
			1	[redacted]	[redacted]		
		Liver metastasis only (%)	0	[redacted]	[redacted]	0.304	N
			1	[redacted]	[redacted]		
		Pralsetinib demonstrates a trend of improved OS (HR [redacted], 95% CI [redacted]) compared to platinum-based chemotherapy +/-					

		pemetrexed, though the result is not significant at the 5% level. Further, pralsetinib demonstrates a statistically significant improvement in PFS and TTD (PFS HR [redacted], 95% CI [redacted]; TTD HR [redacted], 95% CI [redacted]). However, due to the imbalances that remained after adjustment, the comparison was not considered suitable to inform the current appraisal. The motivation for using Flatiron EDM data was the availability of individual patient level data to inform an adjustment in the comparator arm in order to reflect characteristics of a *RET* fusion-positive population. Propensity score matching was also used with similar results as those from weighting. Thus, given in this comparison a sufficient adjustment was not feasible, a naïve comparison represented the most roust methodology available to estimate comparative efficacy of pralsetinib vs. platinum-based chemotherapy +/- pemetrexed in the pre-treated setting (Company Submission, Section B.2.9.4, page 67-80).	
Key issue 7. No correction for crossing curves in probabilistic sensitivity analysis	No	This issue was resolved by the ERG as part of the technical engagement process. As per the Technical Engagement Clarification Call (17th November 2021), no further action is required on this issue.	No further comment
Key issue 8. Constant benefit of	Yes	*Context of treatment waning* Consistently, the topic of a potential waning of treatment effect in NICE oncology appraisals is subject to great uncertainty. In	The ERG reiterates their arguments as stated in the ERG report which mainly evolve around a lack of mature data and agrees with the company that indeed no

pralsetinib assumed without justification and based on immature data		order to design a clinical trial to demonstrate a continued and statistically significant treatment effect benefit at 2, 3, 4, 5 years, the number of subjects needed to be recruited would have to be substantially higher. It would lead to trial delays to recruit the number of patients required (exacerbated by the fact this is a rare mutation) and further delays to wait for trial results to read out. This would result in substantial delays to patient access which would likely be considered undesirable. Therefore, providing clinical trial evidence to adequately test this hypothesis and provide evidence on the exact degree of treatment waning is not feasible and would likely be considered undesirable for patients. Although it is not feasible to provide statistically significant clinical trial evidence, we are able to provide evidence to suggest at the potential likelihood of treatment waning in the remainder of this response. Further, Roche note that the cost-effectiveness results are not sensitive to assumptions surrounding treatment waning for PFS and TTD. In the updated company base case, the difference in the incremental cost-effectiveness ratios (ICERs) between ERG preferred assumptions on PFS/TTD treatment waning and no PFS/TTD treatment waning is [redacted]% across all pairwise comparisons. Therefore, for simplicity the remainder of this response will focus only on treatment waning for OS and assume no treatment effect waning in PFS and TTD. *Treatment effect vs comparators including pembrolizumab in the untreated setting* Treatment effect (and any potential waning) is relative to the comparator treatments. In the UK untreated setting, both	inference should be drawn from the tails of the observed OS curves given low patient numbers. This is exactly the reason that an assumption of no treatment waning seems optimistic. Moreover, there have been many recent appraisals in NSCLC where treatment waning was included, to name a few: - TA654 osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer (2020), the committee concluded here that a 3 to 5 year duration of treatment effect was appropriate, in the absence of more evidence. Of note, this STA was used to inform the utilities in the untreated population in the company base-case, 'given similarities in population'. - TA683, pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (2021), committee preferred waning starting at 3 yrs to reach HR1 at 5 years; - TA724, nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer (2021), treatment effect waning of 3 to 5 years after start of treatment was preferred.

		comparators include pembrolizumab and therefore patients are not on treatment after 2 years due to a stopping rule for pembrolizumab. Therefore, in the untreated setting, treatment waning and a stopping rule on treatment effect enforces the assumption that after a given time point there is no clinical benefit to treatment with pralsetinib over no treatment at all. However, this stopping rule is not in place in the United States and therefore this effect will not be seen in the observed data. *Treatment effect in the observed data* In both the untreated and the pre-treated population for pralsetinib there is observed OS data [redacted] months (Company submission, Section B.2.6.3, Figures 12-13, pages 61-62). However, limited inferences should be drawn from the tails of the curves since the number of patients at risk is low. In the untreated population, there are only [redacted] patients at risk from [redacted] months onwards. In the pre-treated population, there are only [redacted] patients at risk from [redacted] months onwards. For the untreated population, it is possible to examine the relative treatment effect in the observed data by assessing the proportional hazards tests, including the log-negative-log plots (Clarification question C4d response, Figures 3-4, pages 57-69). For the observed data for pralsetinib in comparison to both pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy, there is a continued widening of the treatment effect. In the pre-treated population we are able to use the OS Kaplan-Meier curves to assess the potential treatment waning (Company Submission, Section B.2.9.4, Figures 19, 21, 23, pages 76-78). In all three cases there is a	Given that there is no additional (more mature) data presented on this matter, the ERG considers this issue to remain unresolved. The ERG has run some additional analyses conditional on their updated base-case, varying the point at which treatment waning starts to 3 and 5 years (both lasting for 0 years, so direct decline to HR=1), which together with the already included 2+3 and 2+1 represent a good range of scenarios.

		clear and continued widening of the curves between the pralsetinib OS curves and comparators suggesting no waning of treatment effect in this period. In both populations, OS treatment effect not only appears to not wane, but it appears to widen as time goes on within the observed period. The evidence suggests that there is no waning of the treatment effect in the observed period where there are a reasonable number of patients at risk in the pralsetinib arm. Therefore, the ERG exploratory analysis can be considered implausibly conservative given this assumes that treatment waning begins at 12 months as this is contrary to the observed data. *Implied treatment effect from clinical experts landmark survival predictions* One potential source of evidence to assess the likelihood of potential OS treatment effect waning is to use clinical expert's landmark OS predictions for each treatment to make inferences regarding the duration of the treatment effect for pralsetinib compared to comparators. By calculating the conditional survival from one landmark OS prediction to the next, we are able to infer clinical expert's predictions on the relative treatment effect of pralsetinib vs. comparators and therefore comment on potential treatment waning. An identical conditional survival from one landmark to the next would suggest no treatment effect. A higher conditional survival in the pralsetinib arm compared to comparators would suggest that clinical experts expect a continued OS treatment effect.	

In the untreated setting, clinical experts predict that the conditional survival from 0-3 years and then 3-5 years is higher in the pralsetinib arm vs. comparators. The relative increase is higher in the 3-5 year period compared to 0-3 year period which would suggest no waning of OS treatment effect in the first 5 years of the model and potentially a widening of the OS treatment effect. In the 5-10 year period, the conditional survival in the pralsetinib arm is equal to or lower than comparators.

In the pre-treated setting, conditional survival in the 0-3 year period, 3-5 year period and 5-10 year period is higher in the pralsetinib arm vs. comparators. This would suggest that clinical experts estimate no waning of treatment effect across this time period.

Table 7: Clinical expert landmark survival estimates and implied estimated conditional survival estimates for pralsetinib and comparators in untreated and pre-treated setting

	3 years	5 years	10 years	Conditional survival from 0-3 years	Conditional survival from 3-5 years	Conditional survival from 5-10 years
Untreated						
Pralsetinib	50%	40%	10%	50%	80%	25%
Pembrolizumab +	30%	10%	4%	30%	33%	40%

		pemetrexed + chemotherapy						
		Pembrolizumab monotherapy	25%	8%	2%	25%	32%	25%
		Pre-treated						
		Pralsetinib	35%	20%	7%	35%	57%	35%
		Docetaxel monotherapy	5%	2%	0%	5%	40%	0%
		Docetaxel + nintedanib	5%	2%	0%	5%	40%	0%
		Platinum-based chemotherapy +/- pemetrexed	15%	5%	1%	15%	33%	20%
		*Due to extremely small proportions of patients alive at the 20 year mark, it was not considered reliable to include conditional survival from 10-20 years in the analysis						
		However, it should be acknowledged that clinical experts stated they found the task of estimating landmark survival extremely difficult. These results would be sensitive to small changes in clinician's estimates. Especially given estimates are often						The ERG appreciates the fact that estimating landmark survival is a difficult task for clinical experts but the modelled survival curves were often chosen on the

		rounded to the nearest multiple of 5/10 for simplicity which may impact results. Therefore, this methodology cannot be considered robust. Merely, it is an attempt to address an uncertainty in the data where providing robust long-term evidence is not possible. *Treatment effect in comparable appraisals* In previous appraisals in comparable populations for entrectinib and selpercatinib, no waning of OS treatment effect was modelled in the final model assumptions approved by the committee.(11, 12) *Scenarios exploring varying treatment waning* A number of different treatment waning assumptions and the impact on the ICER was assessed in Table 8. The various assumptions represent the full range of what can be considered realistically plausible assumptions. The ERG's base case assumption is that treatment waning begins soon after or at the exact point that the observed data for pralsetinib finishes ends. This should be considered as a conservative bound for the plausible range of treatment waning scenarios. The ERG's scenario analysis on treatment waning assumes treatment waning begins at the 1-year period. This is not reflected in the observed data and should not be considered in the range of plausible assumptions. Overall, results are not sensitive to assumptions on treatment waning with a relatively small range between the most optimistic and pessimistic assumptions. The results of the cost-effectiveness analysis are not sensitive to OS treatment waning assumptions. Given the paucity of robust long-	basis of these landmark estimates (over statistical fit). The modelled curves turned out to structurally lead to longer overall survival than the landmark estimates for pralsetinib, and (relatively) shorter overall survival for the comparators. The ERG feels that therefore the survival benefit is already exaggerated in the model, and having a sustained effect beyond what was observed would blow up the difference estimated by the clinical experts (which was uncertain to begin with) even more.

term OS evidence, it is not possible to comment confidently on whether there will be a potential waning of OS treatment effect and if so, to what extent that would be. In order to maintain consistency with what was approved by the committee in comparable previous appraisals, the company base case assumes no waning of the OS treatment effect.

Table 8: Scenarios explore impact of varying assumptions on waning OS treatment effect on ICER for pralsetinib (with PAS) vs. untreated and pre-treated comparators

Pralsetinib vs.	ICER (£/QALY) with OS treatment effect waning starting at 2 years and lasting for 3 years	ICER (£/QALY) with OS treatment effect waning starting at 3 years and lasting for 3 years	ICER (£/QALY) with OS treatment effect waning starting at 5 years and lasting for 0 years	ICER (£/QALY) with OS treatment effect waning starting at 5 years and lasting for 5 years	ICER (£/QALY) with no OS treatment effect waning
Pembrolizumab + pemetrexed + chemothera	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		py (untreated)					
		Pembrolizumab monotherapy (untreated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Docetaxel monotherapy (pre-treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Docetaxel + nintedanib (pre-treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Platinum-based chemotherapy +/- pemetrexed (pre-treated)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years
Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14

Conclusion

		• Given the difficulties in estimating long-term waning of treatment effect in oncology appraisals, uncertainties are common • There is no evidence of the beginning of the waning of the treatment effect in the observed data (with sufficient number of patients at risk up to [redacted] months in the untreated setting and [redacted] months in the pre-treated setting) • Inferences from clinical experts' landmark OS predictions estimate that they do not believe there will be treatment waning in the first 5 years of treatment although results cannot be considered robust • No treatment waning was assumed in the two NICE appraisals most comparable to this one • The full range of plausible scenarios have been explored in Table 8. The impact on cost-effectiveness results is not substantial. For consistency with previous appraisals, the company base case assumes no waning of the OS treatment effect	
Key issue 9. Substantial uncertainty in survival curve extrapolations due to immaturity of data	No	*Context of data immaturity* Roche acknowledge a degree of immaturity in the ARROW data. This is a natural consequence of working in a rare mutation such as *RET* which makes recruitment for trials more problematic and therefore limits trial sample size. Further, the low number of events over the [redacted] months of follow up across the untreated and pre-treated settings has resulted in patients' survival being modelled predominantly in the unobserved period in the economic model. This is especially true in the case of OS.	For curve selection, the company addressed an example where under- and over predictions for 3-year overall survival (OS) fall in the range of 5-11 percentage points. Curve selection affects both pralsetinib and comparator survival simultaneously as a result of modelling with Hazard Ratios (HR). Therefore, one should consider the combined under- and over prediction for any fitted curve and corresponding HR, especially when both individual prediction errors are in the opposite direction. Although

		In terms of sample size and maturity of data, the current appraisal is comparable and in some instances favourable to previous NICE appraisals in advanced NSCLC in rare mutations (entrectinib and selpercatinib).(11, 12) *Curve selection* In all cases of curve selection, NICE guidance and best practice was followed to ensure curve selection was as robust and systematic as possible so as to mitigate the impact of curve selection and immaturity of data on results.(13, 14) The ERG note some disparities between clinical expert landmark survival predictions and model predictions (ERG report, Section 4.2.6.11, page 92-93). At the upper end of disparities, absolute over/under prediction ranges from 5-11%. It should be noted that clinical experts in the advisory board expressed great difficulty at accurately placing numerical survival values at landmark points. Further, clinical experts were not simultaneously shown the observed data whilst being asked to make landmark predictions. Therefore, this may lead to some potential inconsistencies between the observed data and the early (e.g. 3-year) landmark survival predictions. The 3-year landmark survival periods are slightly past the end of the observed period where minimal extrapolation has occurred. Clinical experts were shown the predicted HRs from the indirect treatment comparison and commented that they are likely to be observed in clinical practice. Therefore, Roche feel that in this context, absolute	the landmark predictions based on Expert Opinion (EO) lack accuracy, it is the best available data for long-term predictions. In the current example, OS was unfavourable for the comparator (underpredicted by [redacted] percentage points), while simultaneously the OS for pralsetinib was overpredicted by [redacted] percentage points (ERG report, Table 4.6, page 88). In absolute terms, the net combined prediction error was [redacted] percentage points. This shows that, based on EO, one would expect different hazard ratios since the experts expect a smaller gap between the survival curves. The ERG believes both absolute and relative prediction error should be considered, although the ERG agrees that the relative error holds less value when the absolute predictions are close to zero. In relative terms, the under- and over predictions in the current example were [redacted] and [redacted] respectively. The ERG believes that neither the absolute nor relative net combined errors for untreated OS fall in an acceptable range of error, and that even a single absolute error of [redacted] percentage points is questionable.

		errors of 5-11% in some sections of the extrapolation represent an acceptable range of error. The ERG also quote relative over/under prediction of model landmark survival compared to clinical expert predictions. Roche believe that in terms of impact on overall results, the absolute values should take precedence. For example in the hypothetical case of an over prediction of 2% vs 1%, the relative over prediction is 100% which would allude to a large difference however due to the low absolute numbers of patients alive the impact on model results is likely to be minimal. The ERG state "*as it was difficult to identify curves that were optimal for both pralsetinib and comparators, in particular for the untreated population, the ERG refrains from replacing the distributions in the ERG preferred assumptions*" (ERG report, Section 4.2.6, page 93). Roche note that the ERG have not proposed new curve selections. Roche propose that, having followed NICE guidance, in the current context, the current curve selections represent the most robust methodology available to model survival. *ERG calibration approach* Roche note the ERG's scenario of the calibration approach where HRs are calibrated based on clinical experts landmark survival predictions at the 3-year period. This is very sensitive to clinical experts predictions which clinicians stated to be a difficult exercise and were often rounded to multiples of 5/10 and can therefore considered to be	The calibration scenario was implemented by the ERG to investigate alternative plausible HRs and to investigate scenarios where absolute prediction error was diminished. The company argued that the calibration method was less robust, however, the other analyses did not address this additional uncertainty (based on EO prior beliefs) around the HRs. The scenario was reasonable considering that the curve selection was assisted by the same EO prior beliefs. Additional analyses of uncertainty through scenario analysis provided insight in the effects on ICERs which led to more robust conclusions overall. Note that OS is still favourable for pralsetinib in the calibration scenario proposed by the ERG. The ERG considers the issue unresolved.

		approximations instead of an exact science which when translated into HRs can impact results. Roche suggest this is an inferior and less robust methodology than the systematic ITC conducted in the company submission which includes observed data from clinical trials and real world evidence datasets. Given there is a disparity between the HRs from the ITC and the ERG calibrated approach and the ITC outputs were shared with clinical experts at the same advisory board who deemed them to be realistic, the extent to which the ERG calibration approach should be considered in relation to decision making is questionable. *Future evidence* The issue of immaturity in the untreated population will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of *RET* fusion-positive, advanced NSCLC. EQ-5D will be collected in the trial. Recruitment is expected to be completed in [redacted] with results expected in [redacted].	
Key issue 10. Adverse event incidences included in the model potentially	Yes	*Pralsetinib* The inconsistency in sample sizes of the safety populations between those presented in the Company Submission was not an error but relates to the different ARROW trial populations used in each section.	The ERG agrees with the new AE incidences and has taken these into account in their updated analyses. Of note, in the model the ERG received, the updated AE incidences were only implemented in the absolute incidences but not in the percentages and so as a result,

subject to error		The safety population presented in the clinical section (Company Submission, Section B.2.10.2, Table 28, page 98) represents the published MDP population which remains consistent with the rest of the clinical section. The safety population presented in the economic section (Company Submission, Section B.3.3.3, Table 55, page 150) represents the safety/unrestricted efficacy population and was used in the model to align to the population used for efficacy in the same model. In the pralsetinib untreated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. In the pralsetinib pre-treated arm, adverse event costs represent [redacted]% (£[redacted] of £[redacted]) of total costs and [redacted]% ([redacted] of [redacted]) of total QALYs. Therefore, the impact of the selection of either ARROW trial population to use for adverse events in the economic model on cost-effectiveness results is negligible. *Comparators* With regards to comparators, there were some typographical errors in the reporting of the published sources used for adverse event incidence in the Company Submission (Section B.3.3.3, Table 55, page 150) and economic model. • In the case of pembrolizumab monotherapy, the correct reference was provided in the Company Submission but the Company Submission and the economic model both incorrectly report the adverse event incidence of as pneumonia 7% whereas, as per the published source, it	effectively nothing had changed. The ERG therefore has difficulty reproducing the ICERs in Table 10 by applying the company switch for updating AE incidences. The ERG has done an amendment of the model to include the updated AE incidences in the actual cost-effectiveness calculations. Impact is still minor. The ERG considers the issue to be resolved.

should be pneumonia 0% and pneumonitis 3%. This has been updated in Table 9 and the accompanying economic model "ID3875_Pralsetinib for *RET* fusion-positive advanced NSCLC_CEM_TE_ACIC".

- In the case of docetaxel monotherapy, the Company Submission incorrectly referenced Mazieres. (15) The adverse event incidences provided in the Company Submission and economic model represented those provided by Rittmeyer. (16) This has been updated in Table 9. There is no impact on cost-effectiveness results.
- In the case of platinum-based chemotherapy +/- pemetrexed, the Company Submission correctly referenced Ardizzoni. However, the adverse incidences provided in the Company Submission and economic model were incorrectly reported. These have been updated in Table 9 and the accompanying economic model "ID3875_Pralsetinib for *RET* fusion-positive advanced NSCLC_CEM_TE_ACIC".

In the case of pembrolizumab + pemetrexed + chemotherapy and docetaxel + nintedanib, the sources and adverse events presented in the Company Submission align to those used in the economic model and therefore no updates were made.

Table 9: Adverse events included in the economic model (Company Submission, Section B.3.3.3, Table 55, page 150)

	Untreated			Pre-treated			
n, (%)	Pral	Pembro +	Pembro	Pral	Doce	Doce + nin	PBC +/- pem

			chemo	mono		mono		
		ARROW	(17)	(18)	ARROW	(16)	(19)	(20)
		n=404	n=405	n=636	n=404	n=578	n=652	n=112
		Anaemia	[redacted]	74 (18)	0 (0)	[redacted]	33 (6)	0 (0)	6 (5)
		Asthenia	[redacted]	27 (7)	0 (0)	[redacted]	13 (2)	13 (2)	0 (0)
		Blood creatinine phosphokinase increased	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
		Decreased appetite	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
		Decreased neutrophils	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	209 (32)	0 (0)
		Decreased white blood cell count	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	107 (16)	0 (0)
		Diarrhoea	[redacted]	21 (5)	0 (0)	[redacted]	0 (0)	43 (7)	0 (0)
		Disease progression	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
		Dyspnoea	[redacted]	17 (4)	0 (0)	[redacted]	14 (2)	32 (5)	0 (0)
		Fatigue	[redacted]	28 (7)	0 (0)	[redacted]	23 (4)	37 (6)	6 (5)
		Febrile neutropenia	[redacted]	0 (0)	0 (0)	[redacted]	62 (11)	46 (7)	3 (3)
		Hepatitis	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
		Hyperglycaemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)

		Hypertension	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Hypocalcaemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Hyponatraemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	14 (2)	0 (0)	
		Hypophosphataemia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Increased ALT	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	51 (8)	0 (0)	
		Increased AST	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	22 (3)	0 (0)	
		Leukopenia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	19 (3)	9 (8)	
		Lymphocyte count decreased	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Lymphopenia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Malignant neoplasm progression	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Nausea	[redacted]	14 (3)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Neutropenia	[redacted]	65 (16)	0 (0)	[redacted]	75 (13)	79 (12)	13 (12)	
		Pain	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Pleural effusion	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Pneumonia	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	20 (3)	0 (0)	
		Pneumonitis	[redacted]	12 (3)	20 (3)	[redacted]	0 (0)	0 (0)	0 (0)	
		Rash	[redacted]	8 (2)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Sepsis	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	
		Severe skin reactions	[redacted]	9 (2)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)	

Thrombocytopenia	[redacted]	34 (8)	0 (0)	[redacted]	0 (0)	0 (0)	9 (8)
Urinary tract infection	[redacted]	0 (0)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)
Vomiting	[redacted]	16 (4)	0 (0)	[redacted]	0 (0)	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

The impact of the above changes on cost-effectiveness results are presented in Table 10. The changes reduce the ICERs, although the impact can be considered negligible.

Table 10: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared to pembrolizumab monotherapy (untreated) and platinum-based chemotherapy +/- pemetrexed (pre-treated) before and after updated adverse event incidences

Pralsetinib vs.	ICER (£/QALY) before adverse event incidence update outlined in response to Key Issue 10	ICER (£/QALY) after adverse event incidence update outlined in response to Key Issue 10
Pembrolizumab monotherapy (untreated	[redacted]	[redacted]

		Platinum-based chemotherapy +/- pemetrexed (pre-treated) [redacted] [redacted] [redacted] ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14	
Key issue 11. Lack of direct evidence to inform health-related quality of life	Yes	<u>*Summary*</u> Roche acknowledge a degree of uncertainty given utilities were not able to be informed from trial outcomes and there were no existing *RET* fusion-positive advanced NSCLC in the published literature or previous NICE appraisals. This is an unfortunate downside of working in a rare mutation such as *RET.* In this context, we proposed that the best solution is to use health state utility values that have been previously approved by NICE committees in appraisals in patient populations which represent the most comparable to the current appraisal. We note that the ERG report does not suggest any alternative approaches which may indicate that, given the current evidence base with existing uncertainty, they agree that this is the best available approach. Therefore, in the updated company base case, the health state utility values remain as per the initial company submission. <u>*Untreated health state utility values*</u> The ERG reports that the company submission is lacking in explanation for the choice of proxies for the untreated	The fact that no alternative approaches were suggested by the ERG should not be read as a consent to the company's approach. The best possible approach, as stated in the ERG report, would be to collect comparative HRQoL data, and given the current evidence base there is no saying what would the best approach. The company have informed NICE on December 16th that they have observational data indicating that there is indeed a difference between untreated and pre-treated utilities but that the utilities were too high to be validly used in the model. As long as the ERG has not seen these observational data and has no means to evaluate the magnitude of the difference, it is not possible to say whether this has an impact on the appropriateness of the current

<table>
<tr>
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<td>population. We agree that potentially all three sources/populations could arguably represent suitable proxies.

All three populations were approved by previous committees to be the best available evidence to represent their populations. All three populations represented are comparable to the target RET population in this appraisal.

As demonstrated in the Company Submission scenario analysis (Section B.3.8.3, Table 84, page 193-4), we note that the ICER is not sensitive to the selection of the utility proxy. Results have been updated with the updated company base case in Table 11 for the untreated population. The selected proxies in the company base case were chosen as they represent the most comparable population to RET and also represented the scenario with utilities with ICERs in the middle of the range.

Table 11: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared untreated comparators with varying sources for health state utility values
<table>
<tr><th>Pralsetinib vs.</th><th>ICER (£/QALY) updated company base case (PF: 0.794, PD: 0.678)</th><th>ICER (£/QALY) Using alternative utility scenario (21) (PF: 0.784, PD: 0.725)</th><th>ICER (£/QALY) Using alternative utility scenario (22) (PF: 0.780, PD: 0.660)</th></tr>
</table>
</td>
<td>model inputs which were based on previous TAs.

The ERG considers the issue, which was defined as a lack of direct evidence to inform HRQoL, to remain unresolved.</td>
</tr>
</table>

		Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	
		Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14

Pre-treated health state utility values

Roche note the ERG's comment (ERG report, Section 4.2.8, page 97) that the PD health state utility value in the pre-treated population (0.628) is debateable, as it was in ID3743. The value of 0.628 represents a mid-point between the health-related quality of life data collected in LIBRETTO-001 (0.688) and the value approved in TA713 (0.569) (ID3743 Appraisal consultation document, Section 3.13, page 13). (1)

[redacted]

Further, we note that results are not sensitive to the choice of proxy chosen (Table 12).

Table 12: Base-case cost-effectiveness results for pralsetinib (with PAS for pralsetinib) compared pre-treated comparators with varying sources for health state utility values

Pralsetinib vs.	ICER (£/QALY) updated company base case (PF: 0.713, PD: 0.628)	ICER (£/QALY) Using alternative utility scenario (22) (PF: 0.853, PD: 0.659)	ICER (£/QALY) Using alternative utility scenario (11) (PF: 0.672, PD: 0.653)
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14

Future evidence

The health state utility evidence gap in the untreated population will be addressed with the upcoming AcceleRET-Lung clinical trial (10). AcceleRET-Lung is a Phase III, randomised, open-label study of pralsetinib vs. standard of care (including pembrolizumab + pemetrexed + chemotherapy) for first-line treatment of RET fusion-positive, advanced NSCLC. EQ-5D will be collected in the trial. Recruitment is expected to be completed in [redacted] with results expected in [redacted]

Are there any important issues that have been missed in ERG report?	No	--	

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG comment
Additional issue 1: Inclusion of patient's previously treated with a *RET* inhibitor	Section 4.2.3, page 85	No	The ERG report states the population in the economic evaluation is not fully in line with the NICE scope as it does not include patients previously treated with a *RET* inhibitor. Since marketing authorisation is line-agnostic, this group should be included in the economic evaluation.	The ERG was not fully clear on the fact that the indication stated on p12 of the CS was quoting the EMA authorization. The strategy to exclude the population previously treated with a RET inhibitor from the economic modelling seems reasonable. The ERG agrees that the matter is resolved.

			As outlined in the Company Submission (Section B.1.1, page 12). The recent EMA marketing authorisation for pralsetinib does not include patients previously treated with a *RET* inhibitor. "*Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor*" The MHRA licence is anticipated via the EU reliance route and is therefore expected to mirror the above wording. Therefore, the population used in the economic evaluation is reflective of the anticipated marketing authorisation and no amendments will be made to the population used in the economic evaluation. Further, the ERG report states it was not clear how the company excluded patients previously treated with a *RET* inhibitor from the model inputs such as clinical effectiveness, AEs, costs and HRQoL. In the ARROW trial, subjects in Group 6 were previously treated with a *RET* inhibitor. Trial data was used for clinical effectiveness and AEs	

			only in the base-case economic model. ARROW data used in the economic model did not include Group 6 subjects to ensure that the economic model aligned with the marketing authorisation.	
Additional issue 2: Time on treatment falling below PFS for pralsetinib in the untreated population	Section 4.2.6.11, page 93	No	The ERG report notes a separation between the PFS and TTD curves in the respective tails of the untreated population. The ERG hypothesises that this is either because 1) an artefact in the data because of small sample size and immaturity or 2) patients were indeed taken off treatment before progression because of an implicit stopping rule. Roche note that in the graph in question (ERG Report, Figure 4.2, page 94), PFS and TTD closely follow each other for the first [redacted] months of the respective Kaplan-Meier curves. It appears the separation that the ERG is referencing is after the [redacted] month period where there are very few patients at risk (e.g. [redacted] patients at risk in the PFS curve). Indeed, the separation appears to be from just [redacted] subjects who discontinued treatment before progression. Of the two options presented by the ERG, provided a low number of events is driving this, it would allude to option 1) (an artefact in the data because of small sample size and immaturity). Roche would caution inferring too much from a small number of events. The small	The ERG agrees that small numbers would be the most plausible explanation for the observed discrepancy, rather than an implicit stopping rule. This illustrates again the immaturity of the data overall. When TTD is less mature than PFS it would be good to explore alternatives to using observed TTD, which the ERG did in their scenario where TTD = PFS.

			sample size and immature data is in itself an artefact of working in a rare mutation such as *RET*. Roche note the preference of the committee in the selpercatinib appraisal to use TTD to model treatment costs for selpercatinib (Selpercatinib Appraisal Consultation Document, Section 3.11, page 13-15).	
Additional issue 3: Pre-treated supportive care costs	Section 4.2.9.10, page 101-2	Yes	Roche recognises the ERG's concerns regarding the implied inconsistencies in the company approach whereby utilities are lower in the pre-treated setting compared to the untreated setting and health care costs are identical. To address this, the company base case has been updated to arbitrarily assume pre-treated PF supportive care costs are equal to untreated and pre-treated PD supportive care costs (£227.01). The difference between PF and PD supportive care costs is minimal (£202.22 vs. £227.01). The impact of this updated on ICERs in the pre-treated setting is displayed in Table 14 and can be considered negligible.	The ERG agrees this is a reasonable adjustment to make and indeed the impact on the ICER is very minor. The ERG has included this change in their updated analyses.
Additional issue 4: Relative dose	Section 4.2.9.10,	Yes	Currently, the scenario assumes 100% relative dose intensity for pralsetinib and based on a previous submission for sotorasib, a 90%	No further comment, ERG will maintain their base-case with the lowered RDIs in a scenario as they believe for differential RDIs

<table>
<tr>
<td>intensity</td>
<td>page 102</td>
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<td>relative dose intensity for comparators.

Roche have amended the ERG's relative dose intensity scenario analysis below. For pralsetinib, Roche propose the relative dose intensity should be [redacted] (CSR, page 140). For pembrolizumab, Roche propose the relative dose intensity should be 95.6% (NICE TA683, Clarification question B5, page 35). (23) For other comparators including chemotherapy, Roche propose relative dose intensity should be 96.4% (NICE TA683, Clarification question B5, page 35).

In the case of pralsetinib, pembrolizumab and chemotherapy, these relative dose intensities are taken directly from trials and can be considered more robust than the ERG's assumptions.
<table>
<tr><th>ICER pral vs. (untreated)</th><th>ICER pral vs. (pre-treated)</th></tr>
<tr><td>Pembro+chemo: [redacted]</td><td>Doce mono: [redacted]</td></tr>
<tr><td>Pembro mono: [redacted]</td><td>Doce+nin: [redacted]</td></tr>
<tr><td>--</td><td>PBC +/- P: [redacted]</td></tr>
</table>
</td>
<td>to be applied there should be comparative observational data.</td>
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</table>

			Results presented represent include updates made to company base case as part of the technical engagement process as per Table 14 The ICERs presented above are lower than those presented in the ERG scenario analysis and in the company base case. Roche have made the conservative assumption to not include relative dose intensity in the updated company base case.	
Additional issue 5: Proportion of patients receiving pemetrexed	Section 4.2.9.10, page 102	No	The ERG report states there is a lack of justification for the proportion of 63% receiving pemetrexed in the platinum-based chemotherapy +/- pemetrexed comparator. This figure is estimated from an average of feedback from clinical experts in the advisory board. Clinicians were asked to estimate the proportion of *RET* fusion-positive patients in the PD-L1>50% pathway receiving who would go on to receive each of the available treatments in the NICE pathway. The estimate of 63% represents the proportion of patients receiving platinum-based chemotherapy with pemetrexed (including for maintenance) divided by the total proportion of patients receiving platinum-based chemotherapy with or without pemetrexed (including for maintenance). Given this feedback was received from clinical experts, Roche believe this is representative of UK clinical	The ERG considers an estimate from clinical experts in an advisory board to be a less than ideal way to inform a parameter value. Also, the 100% receiving pemetrexed in the study used to inform efficacy all received pemetrexed because it was per protocol (is the ERG's belief and also stated in the ERG report) and so anything could be considered conservative compared to this. The ERG considers the issue to be unresolved.

			practice. The study used to inform efficacy includes 100% of patients receiving pemetrexed. Therefore, the efficacy benefits of pemetrexed are included for 100% of patients (which is not representative of UK practice). However the costs of pemetrexed are included for only 63% of patients (which is representative of UK practice. Therefore, Roche consider this to be a conservative approach.	
Additional issue 6: Testing rate used in scenario analysis	Section 4.2.9.10, page 102	No	The ERG states "*the ERG is unclear what the company exactly means with the proportion of test costs due to pralsetinib, which was arbitrarily set at* [redacted]*"* The costs of *RET* fusion testing that should be attributed towards pralsetinib in the economic model in this appraisal should represent the extent to which the potential approval of pralsetinib by NICE would increase *RET* fusion testing costs. As per the Company Submission (Section B.3.5.5, page 166-7), The Department of Health and NHSE&I have outlined their NHS Long Term Plan where they have committed to offer whole genome sequencing routinely (500,000 whole genomes) by 2023-24. Therefore the company base case assumes the potential approval of pralsetinib by NICE will have no impact on *RET* testing costs.	The ERG appreciates the additional explanation which clarifies the percentage used. In the ACD referred to (section 3.11 page 13 is where the ERG found it), there is no mention of the effect being negligible. It would depend on whether NGS testing for RET fusion would be routine practice in the near future. If not, then the test costs (using the approach proposed by the company or a suitable cost proposed by NHS England as in the selpercatinib appraisal) should be included in the base-case.

			The testing scenario presented by the company was meant to explore the impact of assuming there was some impact of the potential approval of pralsetinib on testing costs. It is difficult to put a percentage figure on this, therefore the figure of [redacted] arbitrarily represents a scenario where the potential approval of pralsetinib increased testing costs by the amount of [redacted] of total patients being tested. The scenario was selected to mirror a key issue in the selpercatinib appraisal. As part of that appraisal, NHSE provided a suitable cost per test to the company which the company accepted and included as part of the economic model (Selpercatinib Appraisal Consultation Document, Section 3.12, page 15). This cost was not presented but it was commented in the committee meeting that the impact of the introduction of this testing cost on results was negligible.	
Additional issue 7: End-of-life, life extension criterion in untreated setting	Section 7, page 122	No	The evidence packaged presented for pralsetinib justifies meeting the life extension criterion in the untreated setting. The ERG report suggests that this is not met due to issues 2, 4 and 5. Issue 2 relates to the selection of comparators which has been addressed in the relevant section of Table 2. Issue 4 relates to the SLR which is only relevant	The ERG acknowledges that the company has separated the issue of whether the end-of-life extension criteria have been met for the treated and untreated settings. In the latest version of the report, the ERG considered the first criterion (life expectancy less than 24 months) to be met. The ERG also acknowledged that based on the

			for the pre-treated setting and not relevant for the indirect comparisons in the untreated setting as the Flatiron EDM dataset was used to inform comparator efficacy in the untreated setting. Issue 5 relates to safety has already been addressed in the relevant section of Table 2. To determine the extent to which pralsetinib extends life over the untreated comparators and therefore meets the life extension criterion, the relevant section of the submission is the untreated indirect treatment comparison for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy (Company Submission, Section B. 2.9.5). Roche note that in Section 3.4 ERG report there was minimal critique of this comparison which seemed to imply confidence in the approach taken. Further, the ERG note that to demonstrate the second criterion is met "*robust comparative data must be provided whereas no MAIC was performed (see Key issue 2)*" (ERG Report, section 7, page 122). This is confusing given in the untreated comparison propensity scoring using IPD has been conducted which, in the ERG's own words is "*superior*" (ERG Report, Section 3.3, page 63) to a MAIC. In the updated company base case, economic model estimates patients in the untreated setting who receive pralsetinib have an undiscounted	results of the economic analysis, that the gain in life years was calculated to be over 2 years versus all comparators. The ERG notes that the company claims that the SLR is "only relevant for the pre-treated setting and not relevant for the indirect comparisons in the untreated setting as the Flatiron EDM dataset was used to inform comparator efficacy in the untreated setting." The ERG notes that there are related problems with inferences drawn from the Flatiron data set (see Key Issue 6) The ERG notes that this statement is difficult to reconcile with the following statement of Document B of the company submission (page 68) "Roche expanded the scope of the SLR in Section B.2.9.1 to identify RCTs conducted in patients with WT NSCLC treated in either the untreated or pre-treated setting". The ERG's concerns regarding the validity of the evidence referred to by the company, (see Key issues 2, 4, 5, and 6). The ERG does not believe that Key Issues 2, 4, 5, or 6 have been sufficiently resolved to overcome these concerns (see remarks

			life expectancy of [redacted] months. This represents a life extension of [redacted] months and [redacted] months over pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy respectively. This is substantially more than the 3 month life extension required to meet the criterion. Clinical experts consulted by Roche in an advisory board were in agreement that pralsetinib would extend life by substantially more than 3 months.	above). As for the gain in life expectancy derived from the economic model, it should be noted that the company's estimates are based on the assumption that there is no waning of the treatment effect. The ERG questions this assumption (see also key issue 8), and so the gain in life expectancy presented here may be overly optimistic, although the ERG agrees that the criterion will be met.
Additional issue 8: End-of-life, life extension criterion in pre-treated setting	Section 7, page 122	No	The evidence packaged presented for pralsetinib justifies meeting the life extension criterion in the pre-treated setting. The ERG report suggests that this is not met due to issues 2, 4 and 5. Each of these issues have been addressed in the responses in relevant sections of Table 2. In the updated company base case, economic model estimates patients in the pre-treated setting who receive pralsetinib have an undiscounted life expectancy of [redacted] months. This represents a life extension of [redacted] months over pre-treated comparators. This is substantially more than the 3 month life	The ERG acknowledges that the company has separated the issue of whether the end-of-life extension criteria have been met for the treated and untreated settings. In the latest version of the report, the ERG considered the first criterion (life expectancy less than 24 months, to be met). The ERG also acknowledged that based on the results of the economic analysis, that the gain in life years was calculated to be over 2 years versus all comparators. The ERG's concerns regarding the validity of the evidence referred to by the company, (see Key issues 2, 4, and 5). The ERG does

			extension required to meet the criterion. Further, the ERG note that to demonstrate the second criterion is met "*robust comparative data must be provided whereas no MAIC was performed (see Key issue 2)*" (ERG Report, section 7, page 122). This is confusing given in the pre-treated comparison against the primary comparator (docetaxel monotherapy), propensity scoring using IPD has been conducted which, in the ERG's own words is "*superior*" (ERG Report, Section 3.3, page 63) to a MAIC. Clinical experts consulted by Roche in an advisory board were in agreement that pralsetinib would extend life by substantially more than 3 months.	not believe that Key Issues 2, 4, or 5 have been sufficiently resolved to overcome these concerns (see remarks above). With regard to modelled life expectancy, as in the untreated setting, estimates from the model are based on the assumption of a continuous benefit of pralsetinib, which the ERG questions. Nevertheless, the ERG agrees that the criterion of a 3 month survival benefit will be met.

Table 13: Additional issues from the ERG report

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 14: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
--	--	--	**Submission base case ICER, pral vs. (untreated)**	**Submission base case ICER, pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono[redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
Key issue 7: PFS vs. OS fix	Without ERG fix	With ERG fix of PFS < OS	No change to base case results	
Key issue 10: Adverse event inconsistencies	As per company submission	As outlined in response to key issue 10 (with typographical errors fixed)	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
Additional issue 3: Pre-treated PD supportive care costs	£202.22	£227.01	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]
ERG fix of cisplatin dose (ERG report, Section 4.2.9, page 102)	Without ERG fix for cisplatin dose	With ERG fix of cisplatin dose	**ICER pral vs. (untreated)**	**ICER pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]

Technical engagement response form

			--	PBC +/- P: [redacted]
Company's base case following technical engagement (or revised base case)	--	--	**Updated base case ICER, pral vs. (untreated)**	**Updated base case ICER, pral vs. (pre-treated)**
			Pembro+chemo: [redacted]	Doce mono: [redacted]
			Pembro mono: [redacted]	Doce+nin: [redacted]
			--	PBC +/- P: [redacted]

Sensitivity analyses around revised base case

Please see Appendix 3.

Appendix 1: Quality assessment

The ERG report states "*There was no mention of any methodological quality assessment for SLR 2*" (ERG report, Section 3.1.4.2.1, page 45). The quality assessment is provided in Table 15.

Table 15: Quality assessment of SLR 2

Criteria		KEYNOTE-042	KEYNOTE-024	KEYNOTE-189	KEYNOTE-021	OAK	LUME-Lung 1	NVALT7	GOIRC 02-2006
WAS RANDOMISATION CARRIED OUT APPROPRIATELY?	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Unclear**	**Yes**
	Rationale	The randomisation schedule was generated by a computerised randomised list generator	Patients were assigned centrally using an interactive voice response system / integrated web-response system	Patients were assigned using an interactive voice-response and web-response system	Patients were assigned using an interactive voice-response system	Patients were assigned using permute block-randomisation via an interactive voice-response system or web-response system	Patients were assigned using interactive third-party telephone via an interactive voice response system, or web-based randomisation via interactive web-based	Method used to assign patients was not reported	Patients were assigned to treatment groups via a minimisation process, through a Web-based system

							response system		
WAS THE CONCEALMENT OF TREATMENT ALLOCATION ADEQUATE?	Decision	**Yes**	**Yes**	**Unclear**	**Unclear**	**No**	**Yes**	**Unclear**	**Yes**
	Rationale	The randomisation schedule was held centrally	The randomisation schedule was held centrally	It was unclear whether the allocation was concealed	It was unclear whether the allocation was concealed	Allocation was unmasked	Treatment allocation was concealed from investigators	It was unclear whether the allocation was concealed	The randomisation schedule was held centrally
WERE THE GROUPS SIMILAR AT THE OUTSET OF THE STUDY IN TERMS OF PROGNOSTIC FACTORS?	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	Rationale	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were generally well balanced between treatment groups†	Demographics and disease characteristics were generally well balanced between treatment groups‡	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups	Demographics and disease characteristics were well balanced between treatment groups
WERE THE CARE PROVIDERS, PARTICIPANTS AND	Decision	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**Unclear**	**No**
	Rationale	This was an open-label study	This was an open-label study	This was a double-blind trial	This was an open-label study	This was an open-label study	This was a double-blind trial	Method of blinding was not reported	This was an open-label study

OUTCOME ASSESSORS BLIND TO TREATMENT ALLOCATION?									
WERE THERE ANY UNEXPECTED IMBALANCES IN DROP-OUTS BETWEEN GROUPS?	Decision	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**Unclear**
	Rationale	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	There was >10% difference in the withdrawal rates between the treatment arms	Rate of withdrawal was similar between the treatment groups	Rate of withdrawal was similar between the treatment groups	The rate of treatment withdrawal was not reported
IS THERE ANY EVIDENCE TO SUGGEST THAT THE AUTHORS MEASURED MORE OUTCOMES THAN THEY	Decision	**No**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
	Rationale	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias	No evidence of reporting bias

REPORTED ?									
DID THE ANALYSIS INCLUDE AN INTENTION-TO-TREAT ANALYSIS? IF SO, WAS THIS APPROPRIATE AND WERE APPROPRIATE METHODS USED TO ACCOUNT FOR MISSING DATA?	Decision	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
	Rationale	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported	ITT analysis included and appropriate; statistical methods for handling missing outcome data were not reported

Abbreviations: ITT, intent to treat.

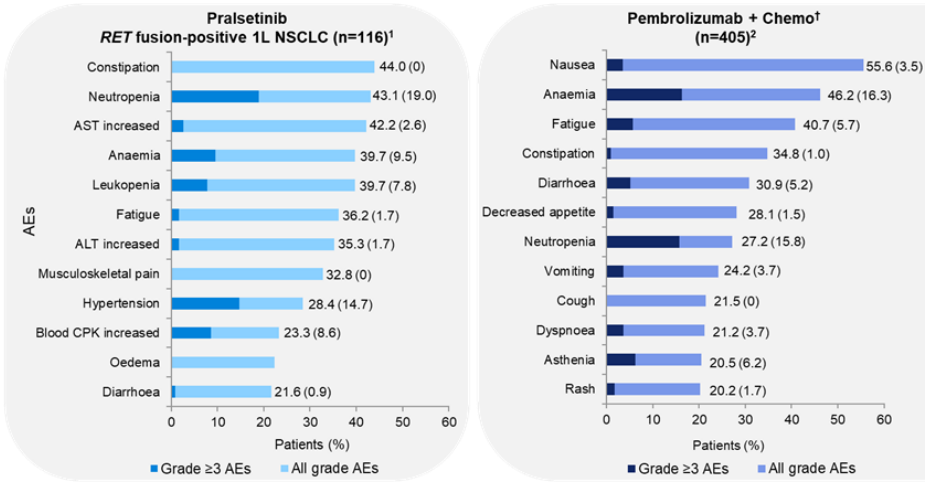
† The percentage of men was higher in the pembrolizumab-combination group than in the placebo-combination group (p=0.04).

‡ Proportionally, more women were enrolled than men (63% of patients in the pembrolizumab plus chemotherapy group and 59% of patients in the chemotherapy group were women).

Appendix 2: Descriptive analysis of the safety profile of pralsetinib (ARROW) vs pembrolizumab + pemetrexed + chemotherapy (KEYNOTE-189 treatment arms) in 1L NSCLC patients

Acknowledging the need of positioning pralsetinib's safety profile in comparison to standard of care and considering the limitations for a formal indirect comparison, a descriptive analysis shows that pralsetinib presents an alternative safety profile compared to pembrolizumab + pemetrexed + chemotherapy and avoids the immune mediated toxicities associated with checkpoint inhibitors.

Figure 2: Safety profile of pralsetinib compared with pembrolizumab + pemetrexed + chemotherapy (data from Keynote-189 trial)



*Most common AEs defined as ≥20% of patients in the active comparator arm are shown. †In patients with previously untreated metastatic non-squamous NSCLC without EGFR or ALK mutations.

AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate transaminase; Chemo, chemotherapy; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung carcinoma; QD, once daily; RET, rearranged during transfection; SoC, standard of care.

1. Grouped preferred terms were used for anaemia, neutropenia, leukopenia, hypertension, musculoskeletal pain, oedema and fatigue.

2. Gandhi L et al. N Engl J Med 2018;378:2078–2092.

The majority of the most common adverse events reported in ARROW were of mild or moderate intensity (Grade 1/2). Regarding haematologic adverse effects, anaemia was observed with a frequency similar to that in the treatment arms of KEYNOTE-189. Neutropenia was reported more frequently in ARROW than in KEYNOTE-189. Nevertheless, both anemia and neutropenia appeared to be manageable by dose modifications and standard practice measures, as no patient in the 1L NSCLC population of ARROW had to discontinue treatment due to these events.

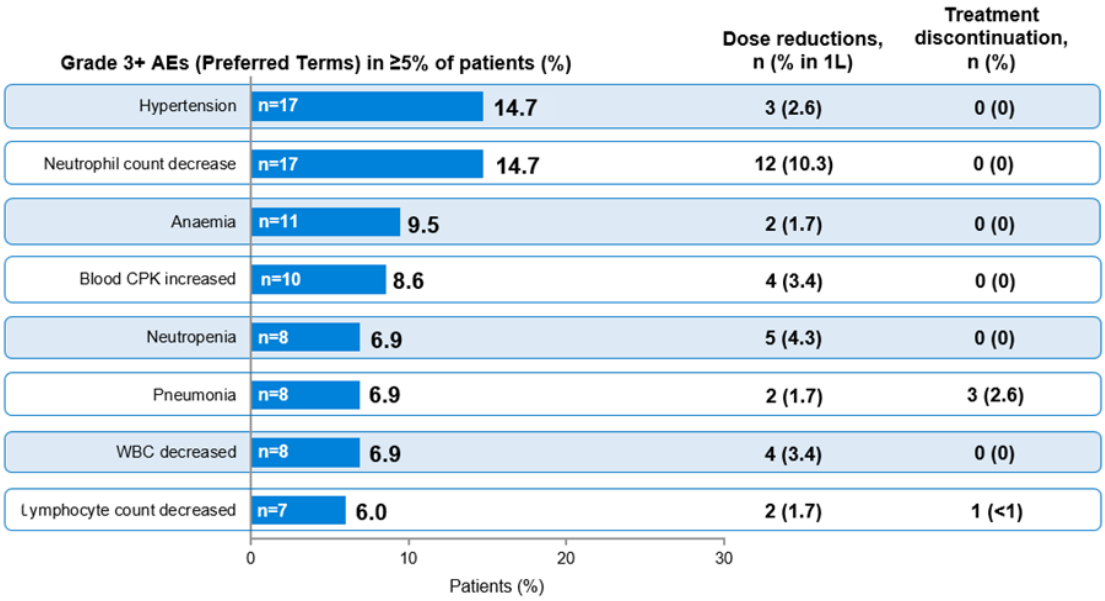
There are three other qualitative differences of note between the pralsetinib safety profile and the KEYNOTE-189 treatment arms in 1L NSCLC: namely hepatic transaminase increases (AST/ALT increased), hypertension and musculoskeletal pain / CPK increase.

- Transaminase elevation observed in ARROW:
    - The vast majority of these events were either Grade 1 or 2
    - No cases of Hy's law or drug-induced liver injury were reported
- Hypertension observed in ARROW:
    - Low rate of patients requiring dose reduction for hypertension
    - No patient needed to discontinue treatment due to hypertension
- Muscular skeletal pain and blood CPK increased observed in ARROW:
    - The events had Grade 1 or 2 intensity in the majority of patient (100% for muscular skeletal pain, 63.0% for blood CPK increase)
    - No patient needed to discontinue treatment due to these events

All of the other events displayed in Figure 2 that were observed after treatment with either pralsetinib or pembrolizumab + pemetrexed + chemotherapy, such as vomiting, occur at similar frequencies across both therapies and are complications of treatment with anti-cancer agents that are routinely managed in the clinic.

In addition, there was a low rate of dose reductions and discontinuations due to grade 3+ events. Dose modifications and standard clinical practice measures enabled the vast majority of patients to continue pralsetinib.

Figure 3: Manageability of grade 3+ events in 1L patients (n=116)



Appendix 3: Updated company base case results

Base-case results

Table 16: Base-case untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 73, page 174

Table 17: Base-case untreated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 18: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab and pemetrexed PAS: ICER (£/ QALY) pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy

	Pemetrexed PAS										
Pembrolizumab PAS	**0%**	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
0%	[redacted]										
10%	[redacted]										
20%	[redacted]										
30%	[redacted]										
40%	[redacted]										
50%	[redacted]										
60%	[redacted]										
70%	[redacted]										
80%	[redacted]										
90%	[redacted]										
100%	[redacted]										

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 74, page 175

Table 19: Base-case untreated results (with PAS for pralsetinib) against untreated comparators with varying pembrolizumab PAS: ICER (£/ QALY) pralsetinib vs. pembrolizumab monotherapy

Pembrolizumab PAS	ICER (£/ QALY) pralsetinib vs. pembrolizumab monotherapy
0%	[redacted]
10%	[redacted]
20%	[redacted]
30%	[redacted]
40%	[redacted]
50%	[redacted]
60%	[redacted]
70%	[redacted]
80%	[redacted]
90%	[redacted]
100%	[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.1, Table 75, page 176

Table 20: Base-case pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.7.2, Table 76, page 177

Table 21: Base-case pre-treated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Probabilistic sensitivity analysis

Table 22: PSA untreated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1, Table 77, page 177

Table 23: PSA untreated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 4: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab + pemetrexed + chemotherapy

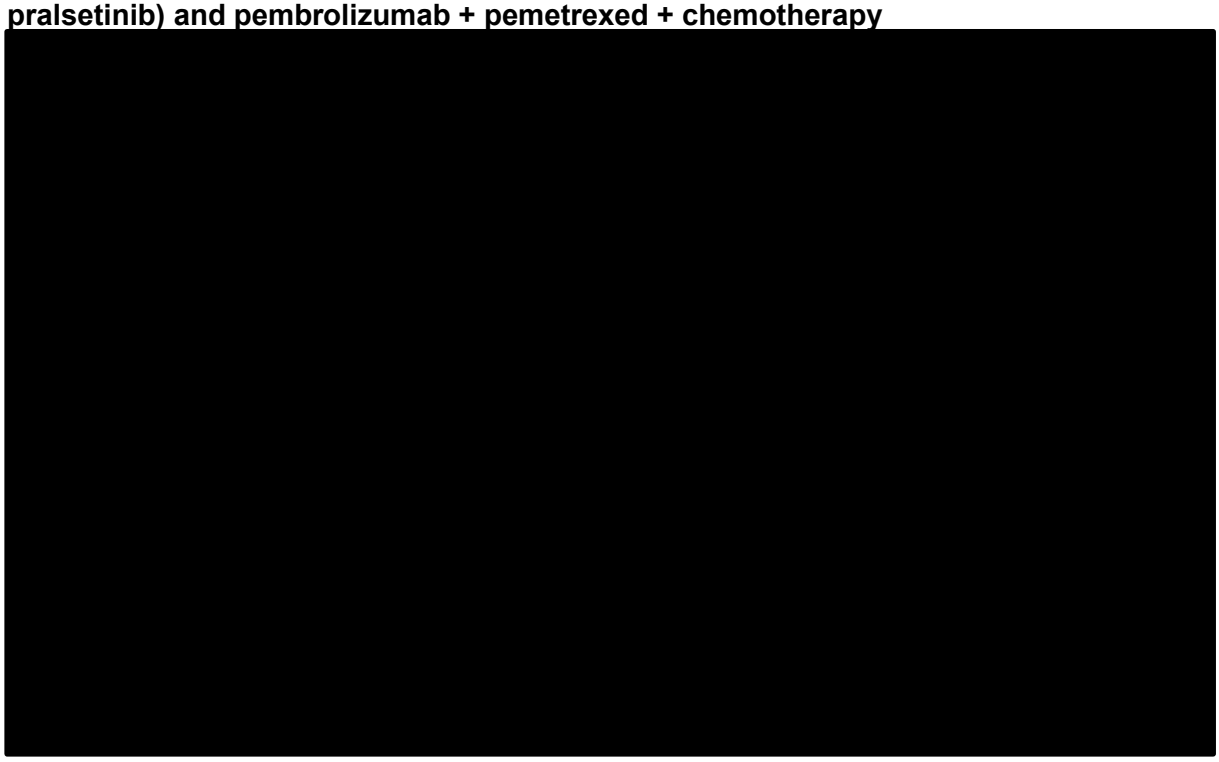


Figure 5: Cost-effectiveness plane untreated results of pralsetinib (with PAS for pralsetinib) and pembrolizumab monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.1, Figure 61, page 179

Figure 6: Untreated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.1, Figure 62, page 179

Table 24: PSA pre-treated results (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Table 78, page 180

Table 25: PSA pre-treated results fully incremental analysis (with PAS for pralsetinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/ LYG)	ICER (£/ QALY)	ICER to baseline (£/ QALY)
Platinum-based chemotherapy +/- pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 7: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel monotherapy

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Figure 63, page 180

Figure 8: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and docetaxel + nintedanib

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Figure 64, page 181

Figure 9: Cost-effectiveness plane pre-treated results of pralsetinib (with PAS for pralsetinib) and platinum-based chemotherapy +/- pemetrexed

PAS, patient access scheme; QALYs, quality-adjusted life years
Corresponding to Company Submission, Section B.3.8.1.2, Figure 65, page 182

Figure 10: Pre-treated cost-effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators

PAS, patient access scheme; QALYs, quality-adjusted life years

Corresponding to Company Submission, Section B.3.8.1.2, Figure 66, page 182

Deterministic sensitivity analysis

Untreated

Table 26: Untreated DSA for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%

Cost per first admin.- pemb + pem + chemo	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- pemb + pem + chemo	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.794	0.780	[redacted]	0.807	[redacted]	95% CI
PD health state utility value	0.678	0.542	[redacted]	0.814	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 79, page 183

Figure 11: Untreated tornado plot for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy (with PAS for pralsetinib)

PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Figure 67 page 184

Table 27: Untreated DSA for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- pem mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.79	0.78	[redacted]	0.81	[redacted]	95% CI
PD health state utility value	0.68	0.54	[redacted]	0.81	[redacted]	95% CI

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 80 page 185

Figure 12: Untreated tornado plot for pralsetinib vs. pembrolizumab monotherapy (with PAS for pralsetinib)

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.1, Figure 68 page 186

Pre-treated

Table 28: Pre-treated DSA for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce mono	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.2, Table 81 page 186-187

Figure 13: Pre-treated tornado plot for pralsetinib vs. docetaxel monotherapy (with PAS for pralsetinib)

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.2, Figure 69 page 188

Table 29: Pre-treated DSA for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

Cost per first admin.- pralsetinib and doce mono	192.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib and doce mono	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per simple chemo.- doce + nin	241.06	192.85	[redacted]	289.27	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.72	0.71	[redacted]	0.72	[redacted]	95% CI
PD health state utility value	0.63	0.50	[redacted]	0.75	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.2, Table 82 page 188-189

Figure 14: Pre-treated tornado plot for pralsetinib vs. docetaxel + nintedanib (with PAS for pralsetinib)

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.2, Figure 70 page 190

Table 30: Pre-treated DSA for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

Parameter	Base-case value	Lower value	Lower value ICER	Higher value	Higher value ICER	Justification
BSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI
HR TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95% CI

Cost per first admin.- pralsetinib	195.00	156.00	[redacted]	234.00	[redacted]	+/-20%
Cost per subsequent admin.- pralsetinib	15.00	12.00	[redacted]	18.00	[redacted]	+/-20%
Cost per first admin.- PBC +/- pem	370.68	296.54	[redacted]	444.82	[redacted]	+/-20%
Cost per subsequent admin.- PBC +/- pem	332.13	265.70	[redacted]	398.56	[redacted]	+/-20%
Individual PF/PD health state costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual PF/PD health state costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: units costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual terminal care costs: resource use	Many	Many	[redacted]	Many	[redacted]	+/-20%
Individual adverse events: unit costs	Many	Many	[redacted]	Many	[redacted]	+/-20%
Subsequent treatment duration	Many	Many	[redacted]	Many	[redacted]	+/-20%
PF health state utility value	0.713	0.712	[redacted]	0.715	[redacted]	95% CI
PD health state utility value	0.628	0.502	[redacted]	0.754	[redacted]	+/-20%

BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; HR, hazard ratio; OS, overall survival; PD, progressed disease; PF, progression-free; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme
Corresponding to Company Submission, Section B.3.8.2.1, Table 79, page 183

Figure 15: Pre-treated tornado plot for pralsetinib vs. platinum-based chemotherapy +/- pemetrexed (with PAS for pralsetinib)

PAS, patient access scheme

Corresponding to Company Submission, Section B.3.8.2.1, Figure 67 page 184

Scenario analysis

Table 31: Untreated and pre-treated scenario analysis

Parameter	Base-case	Scenario	Untreated – ICER (£/ QALY) pral vs.		Pre-treated – ICER (£/ QALY) pral vs.		
			Pemb + chem.	Pemb. mono	Doce mono	Doce + nin	PBC +/- pem
Base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	25-years	5-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate – costs and QALYs	3.50%	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Half cycle correction	Enabled	Disabled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated OS curve selection for pralsetinib	Weibull	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated OS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated PFS curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated TTD curve selection for pralsetinib	Exponential	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (adjusted IPTW)	As per Flatiron analysis adjusted using matching as per Flatiron technical report (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming no adjustment for metastases)	As per Flatiron analysis assuming adjustment for metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case (assuming only ECOG PS 0-1 in eligibility)	As per Flatiron analysis (no ECOG PS restrictions in eligibility criteria)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemb + chem. and pemb. mono and HRs for OS, PFS, TTD	As per Flatiron analysis base case	As per naïve comparison (Section B.2.9.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib HRs for OS, PFS, TTD	Assumed equal to docetaxel mono	As per naïve comparison	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method for modelling treatment duration	TTD as per ARROW	Assumed equal to PFS as per ARROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule for pembrolizumab	2-year stopping rule	No stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients in PBC +/- pemetrexed arm receiving pemetrexed	62.8% as per UK clinical practice	100% as per clinical efficacy study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RET fusion testing costs	Not included	Included as per Section B.3.5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Untreated health state utility values	PF: 0.794 PD: 0.678	PF: 0.784 PD: 0.725	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.794 PD: 0.678	PF: 0.780 PD: 0.660	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated health state utility values	PF: 0.713 PD: 0.628	PF: 0.853 PD: 0.659	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PF: 0.713 PD: 0.628	PF: 0.672 PD: 0.653	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation
Corresponding to Company Submission, Section B.3.8.2.1, Table 84, page 193-194

Appendix 4: Quantitative bias analysis

Summary of quantitative bias analysis

Roche have recently been exploring quantitative bias analysis in a collaboration with NICE. As part of that collaboration, NICE have requested the inclusion of quantitative bias analysis as part of this appraisal to assess its acceptability and impact on the appraisal

Synthetic control arms are increasingly being used for regulatory and payer submissions involving single arm clinical trials, such as for cancers with rare genetic driver mutations like KRAS and *RET* where a concurrent comparator arm may be infeasible or unethical. (25) Naturally, the possibility that effect estimates or risks can differ systematically between trials and routine clinical practice can be concerning to decision-makers. An approach to mitigate the concerns of bias in non-randomized comparisons is using quantitative bias assessment, which can quantify the strength of plausible sources of biases, such as bias from unmeasured confounding that would be required to nullify or reverse the conclusions of the study. (26) For example, if ECOG status is missing for a large proportion of patients in real-world data, it may be useful to report effect estimates over a range of assumptions about missing ECOG, including non-random missingness. Indeed, the UK NICE has recommended the use of quantitative bias assessment and other sensitivity analyses such as negative/positive controls to support RWE. (27) Although the use of these approaches in non-randomized studies is currently limited, we anticipate that they will see increasing use as pre-specified analyses in the future as interest in RWE inevitably grows. Having done our best to mitigate bias through careful selection and execution of statistical techniques, consider that if the residual bias does not unfairly favour the candidate treatment over the control or standard of care, then the chief question in comparative effectiveness studies can still be answered in a valid manner.

Quantitative bias analysis was conducted on the indirect treatment comparison for pralsetinib vs. pembrolizumab + pemetrexed + chemotherapy and pralsetinib vs. pembrolizumab monotherapy in the untreated setting where comparators were informed with data from the Flatiron EDM dataset (Company Submission, Section B.2.9.5, page 80-91).

Quantitative bias analysis for missing data assumptions about baseline covariates

To assess the sensitivity of our results to missing data assumptions, HRs were computed under three scenarios:

1. Baseline confounder data missing completely at random (MCAR) – Using complete case analysis where patients with a missing value for one or more baseline confounders were excluded. Complete-case analysis was used for the main analyses reported in the main document. In the general case for real-world scenarios, MCAR is a simplistic assumption of missingness.

2. Baseline confounder data missing at random (MAR) – Using multiple imputation (MI) of missing data for baseline confounders

3. ECOG PS missing not at random (MNAR) – To account for the robustness of our findings to the non-negligible amounts of missing ECOG performance scores (PS), using multiple imputation with delta adjustment (see below), where missing data for baseline confounders was imputed under the assumption that patients with a missing ECOG PS in the comparator arm to pralsetinib could have been poorer than expected under MAR, and therefore explained away some of the observed differences in outcomes.

MAR and MNAR analyses required multiple imputation, which was performed using chained equations.(28) For multiple imputation, 20 imputed datasets were generated to account for uncertainty and random error in the prediction of missing values. N=20 was chosen to balance computational efficiency with theoretical guidelines for multiple imputation from Graham et al given the proportion of missing values in our data.(29) Predictive mean matching and logistic regression were used to impute

continuous and dichotomous variables except ECOG PS, which used ordered proportional-odds logistic regression. For congeniality, all variables used in propensity score estimation and Cox regression were included in multiple imputation, including outcome variables. Mean observed ECOG PS at any time was included as auxiliary variables to improve prediction accuracy. HRs and standard errors were computed for each imputed dataset separately and then pooled using Rubin's rules to account for intra- and inter-imputed dataset variance.(30) For median survival times, simple mean values for 95% CI were calculated.

For δ adjustments, δ was an additive term applied to the ordered logistic regression model for ECOG PS representing $\log \frac{p(Y \leq j)}{p(Y>j)}$. (31, 32) For the adjustments, fixed constant values of δ of 1, 0, -1, -2, -3, -4 and -5 were added to the ordered logistic regression imputation model for ECOG PS. As shown in Figure 16, positive values for δ probabilistically shifted predicted ECOG PS to be more favourable than expected under MAR, i.e., assigning a lower ECOG PS than predicted given observed covariates, for those missing ECOG PS. Conversely, a negative δ randomly shifted predicted ECOG PS to be poorer than expected under MAR.

Twenty datasets were multiply imputed for each setting of the δ parameter. At δ=-3, for example, amongst those in the pembrolizumab arm lacking baseline PS (approximately 23% of all patients), only 4% of patients were predicted to have an ECOG PS of 0, as opposed to 18% amongst all patients with a non-missing ECOG PS. For interpretability of results, instead of the log-odds defined by δ, we report the resulting mean shift in imputed ECOG PS for each setting of δ. The delta value of zero represents standard multiple imputation.

Table 32: Hazard ratios comparing pralsetinib vs pembrolizumab monotherapy and pralsetinib vs pembrolizumab + pemetrexed + chemotherapy using multiple imputation. Consistent with eligibility criteria for this study, patients with imputed ECOG PS >1 were excluded

Exposure	Reference	HR
Pralsetinib (n=71)	Pembrolizumab (Mean n=920)	[redacted]
Pralsetinib (n=71)	Pembro + chemo (Mean n=1635)	[redacted]

Figure 16: Distribution of ECOG PS by delta (δ). Note that the sample sizes for patients includes those with both missing and non-missing baseline ECOG PS, but for the analyses, patients with ECOG PS >1 were excluded as this was an eligibility criterion.

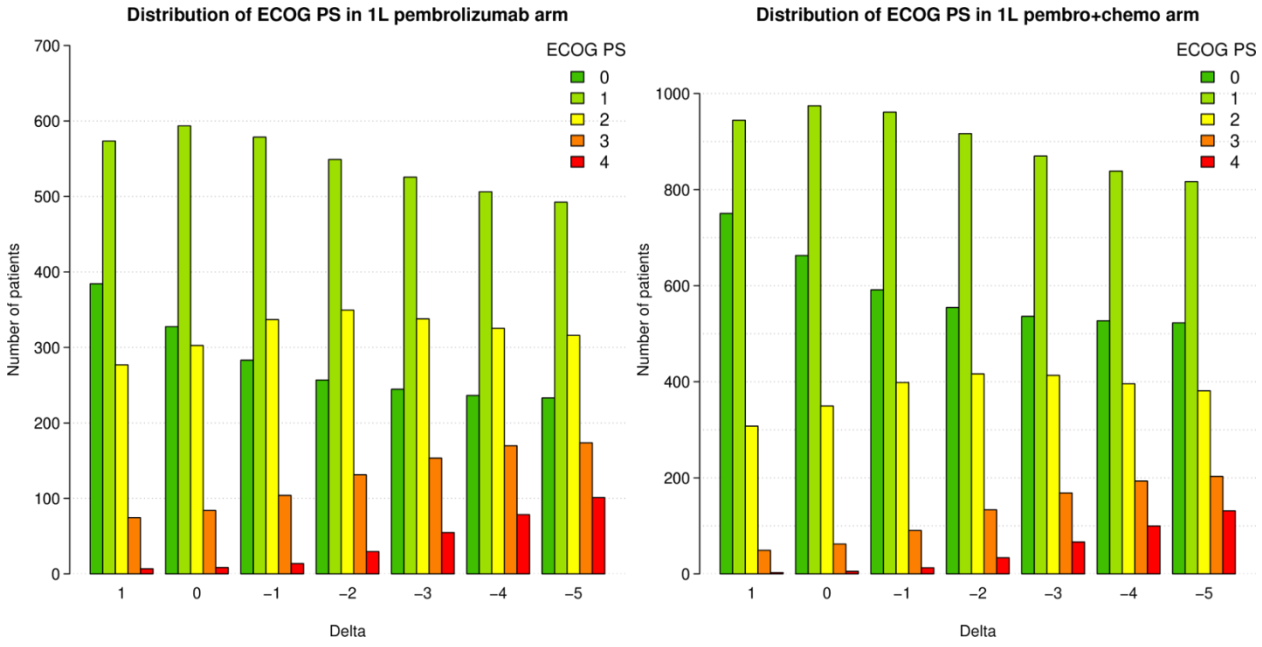
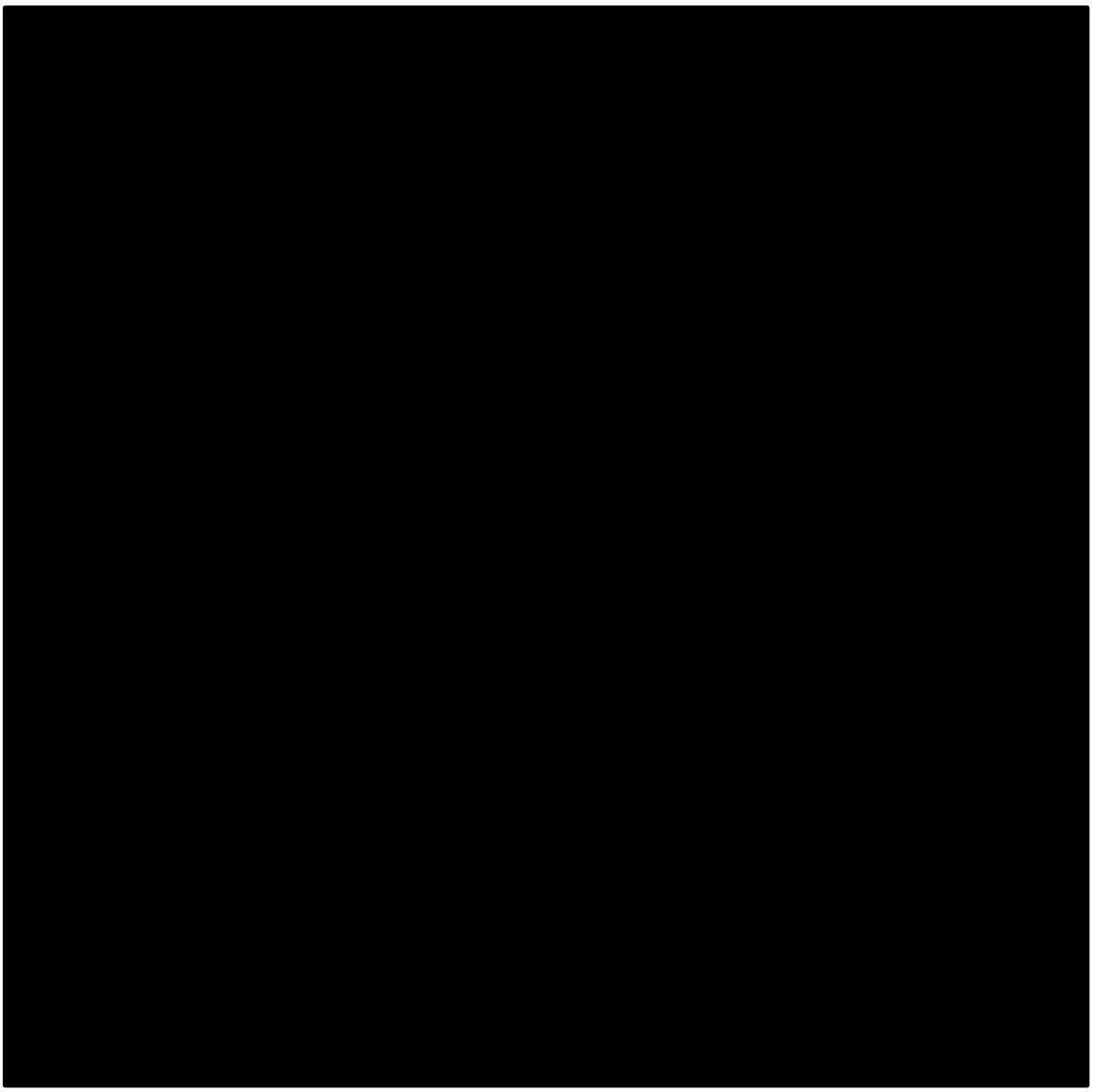


Figure 17 shows that negative values for δ shifted hazard ratios progressively in the direction towards the null and median survival times for the comparator arms to longer times, until achieving a plateau at δ=-3. Also shown in Figure 17, no tipping points could be identified for untreated pembrolizumab monotherapy or untreated pembrolizumab + pemetrexed + chemotherapy, indicating that our results are robust to deviations from random missingness for baseline ECOG PS. Furthermore, our results were robust in general to missingness assumptions for measured baseline covariates as shown with δ=0 under standard multiple imputation compared to the main analyses.

Figure 17: Tipping point analysis for missing baseline ECOG PS. Delta (δ) values of +1, 0, -1, -2, -3 and -4 corresponded to the observed mean ECOG PS shifts shown below of -0.35, +0, +0.44, +0.89, +1.30 and +1.61. MST represents the median survival time in months for the comparator to pralsetinib, either

pembrolizumab monotherapy or pembrolizumab + pemetrexed + chemotherapy. MST for pralsetinib was not estimable.



Quantitative bias analysis for unmeasured confounding

This analysis examines the effect of unmeasured confounding that would be required to nullify or reverse the conclusions of this study. We assume for interpretability that a hypothetical binary confounder U underlies the residual and/or unmeasured confounding on the estimated treatment effects from this study. By assessing how strong of a confounder U would have to be to nullify or reverse our conclusions, we

can measure the robustness of this study. To do this, we calculate the bias B resulting from U as a function of

1. association of U with the outcome on the risk ratio scale (RRUD), and
2. imbalance of U between treatment arms on the risk ratio scale (RREU) as in VanderWeele et al. (2017). (33)

Because only risk ratios are handled, hazard ratios were converted to approximate risk ratios using the square-root transformation from VanderWeele (2017). (34) HRs from multiple imputation reported in Table 1 were used here for the bias plots for the worst-case scenario.

In Figure 18 and Figure 19, we plot bias curves for untreated pralsetinib versus pembrolizumab monotherapy and untreated pralsetinib vs pembrolizumab + pemetrexed + chemotherapy comparisons. For example, the black curve at the point estimate of [redacted] (adjusted risk ratio [redacted]) in Figure 18 plots the range of values for the association of U with survival and treatment assignment that would be needed to nullify our conclusions, i.e., that the unconfounded effect estimate adjusted for U would equal 1 on the risk ratio scale for pralsetinib vs pembrolizumab monotherapy comparison.

To assess the plausibility of unmeasured confounding, we also plot the observed associations of measured confounders with survival and treatment assignment from this study along with 95% CIs. The bias plot shows that on the continuum of uncertainty in our results due to residual/unmeasured confounding, we expect that our results are robust when considering that important well-measured potential baseline confounders such as age and smoking history were neither highly prognostic of survival nor (except smoking history) highly imbalanced between treatment groups.

Figure 18: Bias plot for unmeasured confounding for untreated pembrolizumab monotherapy comparison ([redacted]). This graph plots unconfounded treatment effect estimates as risk ratios (ARR; adjusted risk ratio) after adjusting for a hypothetical unmeasured binary confounder over a range of confounder-exposure and confounder-outcome associations on the risk ratio scale. The colours map the strength of an unmeasured confounder (x and y axes) to the robustness of this study's conclusions (colour gradient). The worst-case strengths of measured baseline confounders are shown.

Figure 19: Bias plot for unmeasured confounding for 1L pembrolizumab comparison ([redacted]). This graph plots unconfounded treatment effect estimates as risk ratios (ARR; adjusted risk ratio) after adjusting for a hypothetical unmeasured binary confounder over a range of confounder-exposure and confounder-outcome associations on the risk ratio scale. The colours map the strength of an unmeasured confounder (x and y axes) to the robustness of this study's conclusions (colour gradient). The worst-case strengths of measured baseline confounders are shown.

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Addendum to:

Pralsetinib for RET fusion-positive advanced non-small cell lung cancer [ID3875]

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Addendum to ERG report

This addendum presents the cost-effectiveness results of pralsetinib for RET fusion-positive advanced non-small cell lung cancer. In this addendum, the ERG have re-run their original analyses with the adjustments the company made to their model in response to technical engagement, i.e. with corrected adverse event incidences and an adjustment to the progression free health state costs for the pre-treated population.

In response to the additional treatment waning scenarios the company presented in their response to technical engagement, the ERG also presents two additional scenarios on treatment waning.

Table 1: Deterministic and probabilistic CS base-case and ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Updated deterministic CS base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4* Matter of judgement: Treatment waning OS, assuming start waning at 2 years over a period of 3 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Updated deterministic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated probabilistic ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PSA = patient access scheme; QALYs = quality-adjusted life years

* fixing errors 2 and 3 no longer apply as they have been incorporated in the updated CS base-case

Table 2: Deterministic scenario analyses (conditional on updated ERG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Updated ERG base-case					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 1: Treatment waning OS, assuming time till waning 1 years over 2 years					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 2: Calibrated hazard ratios for comparators at 3 years for OS and PFS untreated and pre-treated populations					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG scenario 3: TTD = PFS (for all TTD curves (except treatment cut-off))					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario 4: Relative dose intensity = 90% for all treatments					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALYs = quality-adjusted life years; TTD = time to treatment discontinuation					

Table 3: Additional deterministic scenarios run by the ERG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Additional ERG scenario 1: Treatment waning 3 + 0					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional ERG scenario 2: Treatment waning 5 + 0					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALYs = quality-adjusted life years; TTD = time to treatment discontinuation					

Table 4: Additional probabilistic scenarios run by the ERG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG scenario 2: Calibrated hazard ratios for comparators at 3 years for OS and PFS untreated and pre-treated populations					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional ERG scenario 2: Treatment waning 3 + 0					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional ERG scenario 2: Treatment waning 5 + 0					
Untreated population					
Pralsetinib 1L	[redacted]	[redacted]			
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Pralsetinib 2L	[redacted]	[redacted]			
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALYs = quality-adjusted life years; TTD = time to treatment discontinuation

Table 5: Fully incremental probabilistic updated ERG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Probabilistic updated ERG base-case					
Untreated population					
Pembrolizumab	[redacted]	[redacted]			
Pembrolizumab + pemetrexed + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-treated population					
Docetaxel	[redacted]	[redacted]			
Platinum-based chemotherapy 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pralsetinib 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years					

Figure 1: Untreated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators, updated ERG base-case

[redacted]

Figure 2: Pre-treated cost effectiveness acceptability curve of pralsetinib (with PAS for pralsetinib) and comparators, updated ERG base-case