NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

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 Products

2. **Clarification questions and company responses**
   a. Company response to clarification
   b. Further responses to clarification

3. **Patient group, professional group and NHS organisation submission** from:
   - British Thoracic Oncology Group, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians and Royal College of Radiologists – *joint submission, endorsed by clinical experts:*
     - Dr Yvonne Summers – Consultant Medical Oncologist & Honorary Senior Lecturer, The Christie Hospital NHS Trust and Manchester University NHS Foundation Trust
     - Dr Matthew Krebs – Clinical Senior Lecturer in Experimental Cancer Medicine and Honorary Consultant in Medical Oncology, The University of Manchester and The Christie NHS Foundation Trust

   Expert personal perspectives from:

   Two clinical experts endorsed the joint statement from BTOG-NCRI-ACP-RCP-RCR (see above)

4. **Evidence Review Group report** prepared by BMJ Group

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

6. **Evidence Review Group report – erratum**

7. **Draft Technical Report**

8. **Technical engagement response from Roche Products**

9. **Technical engagement responses from experts:**

- Dr Yvonne Summers – clinical expert, nominated by Roche Products

10. Technical engagement responses from consultees and commentators:

- British Thoracic Oncology Group, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians and Royal College of Radiologists – joint response

11. Company new evidence submission at technical engagement from Roche Products

12. Evidence Review Group critique of company response to technical engagement prepared by BMJ Group

13. Evidence Review Group critique of company new evidence

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

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer

[ID1541]

Document B

Company evidence submission

June 2019

File name	Version	Contains confidential information	Date
ID1541_Entrectinib ROS1_NICE STA_Document B_AICCIC	1.0	Yes	3 June 2019

Contents

Tables and figures

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, but entrectinib is intended for use in the first- or second-line setting, as summarised in Table 1.

It is also important to acknowledge upfront that we are actively seeking Cancer Drugs Fund (CDF) funding for entrectinib, which impacts the relevance of comparators. While we understand the National Institute for Health and Care Excellence (NICE) position statement on including treatments funded through the CDF as comparators in technology appraisals; where the technology under appraisal is directly targeting CDF reimbursement, a CDF comparison is arguably the most appropriate from a National Health Service (NHS) funding perspective. Furthermore, while NICE cannot consider crizotinib as standard of care in the context of comparator technology appraisals, crizotinib is the recommended first-line treatment in the recently published NICE pathway for the management of advanced non-squamous non-small-cell lung cancer (NSCLC) for ROS1-positive NSCLC[1], and is considered standard of care in this setting by the clinical community.[2, 3] Considering these factors and recognising a [redacted] (see Section B.2.11) the inclusion of a scenario analyses comparing entrectinib with crizotinib has been sanctioned by NICE.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer	People with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer	N/A
Intervention	Entrectinib	Entrectinib	N/A
Comparator(s)	Untreated disease: • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) – with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) – with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • Single agent chemotherapy with a third generation drug for people who cannot tolerate platinum-based therapy	• Crizotinib • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) – with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment	Entrectinib is intended for use in the first- or second-line setting and is directly targeting CDF reimbursement. Crizotinib is the most clinically relevant comparator in this setting, and as a CDF funded treatment, is arguably the most relevant comparator from a funding perspective. Crizotinib is therefore included alongside pemetrexed plus platinum as relevant comparators to the decision problem. Of the other comparators included in the final scope, those detailed below are not considered relevant to the decision problem for the reasons noted: Chemotherapy in combination with platinum is not commonly used in patients with non-squamous histology where ROS1 arises most frequently. The committee conclusion in TA529

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	After previous chemotherapy treatments: • Docetaxel, with (for adenocarcinoma histology) or without nintedanib		was that platinum-doublets were not relevant comparators. Newly diagnosed ROS1-positive NSCLC patients are generally young and physically fit and therefore unlikely to be treated with single agent chemotherapy that is reserved for people who cannot tolerate platinum-based therapy. The committee conclusion in TA529 was that single agent chemotherapy was not a relevant comparator. Docetaxel, with (for adenocarcinoma histology) or without nintedanib is only used after previous chemotherapy treatments, that is, in the third-plus setting. It is therefore considered as part of subsequent therapy but not as a direct comparator to this appraisal.
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 final scope.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, consideration will be given to subgroup based on the presence or absence of brain metastases.	Consideration of the clinical effectiveness is given to subgroup based on the presence or absence of brain metastases.	The limited overall size of the trial population and the smaller CNS population prohibits separate comparative effectiveness and cost-effectiveness analysis of this subgroup.

Key: CDF, Cancer Drugs Fund; ECOG PS, Eastern Cooperative Oncology Group performance status; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer.

B.1.2. Description of the technology being appraised

A summary description of entrectinib is provided in Table 2. The draft summary of product characteristics (SmPC) for entrectinib is provided in Appendix C. The European public assessment report will be shared as soon as it is available.

Table 2: Technology being appraised

UK approved name and brand name	Entrectinib (RO7102122; formerly known as RXDX-101, and NMS-1191372)
Mechanism of action	Entrectinib is an oral, CNS-active, potent inhibitor of the ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the gene *ROS1*). Entrectinib is also a potent inhibitor of the tyrosine kinases tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC; encoded by the genes *NTRK1*, *NTRK2* and *NTRK3*, respectively) and ALK; encoded by the gene *ALK*).
Marketing authorisation status	The EMA regulatory submission was made in [redacted] and marketing authorisation is anticipated in [redacted].
Indications and any restriction(s) as described in the draft summary of product characteristics (SmPC)	The anticipated indication of interest is: [redacted] A further anticipated indication of interest to appraisal ID1512 is: [redacted]
Method of administration and dosage	600mg given orally (as three 200mg capsules), once daily Treatment is recommended until disease progression or unacceptable toxicity.
Additional tests or investigations	No additional tests or investigations are needed. While ROS1-positive status must be established prior to initiation of entrectinib therapy, ROS1 testing is included in the 2019/2020 National Genomic Test Directory for Cancer.[4]
List price and average cost of a course of treatment [a]	**List price**: [redacted] for a 90-pack volume of 200mg capsules and [redacted] per 30 tablet pack **Average cost of a course of treatment:** £[redacted] with list price

	Average cost of a course of treatment: £[redacted] with PAS
Patient access scheme	[redacted]
Key: ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; CNS, central nervous system; EMA, European Medicines Agency; NSCLC, non-small-cell lung cancer; PAS, patient access scheme; SmPC, summary of product characteristics. **Notes:** [a], based on median ToT. **Source:** Entrectinib draft SmPC[5]	

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

Disease overview

Brief overview of disease

Lung cancer is the third most common cancer in the UK, accounting for 13% of all cancer cases,[6] with 39,001 cases reported in England and Wales in 2016.[7] NSCLC is the most common type of lung cancer, accounting for 88.5% of lung cancers in England and Wales in 2016.[7] There are three histological subtypes of NSCLC: squamous-cell carcinoma, large-cell carcinoma and adenocarcinoma, which is the most common.[8] Adenocarcinoma and large-cell carcinoma are classified as non-squamous histological subtypes of NSCLC.

NSCLC is staged according to the tumour, node and metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC), which is used to assign patients with an overall disease stage of 0, I, II, III or IV.[9] The majority of lung cancers are diagnosed at an advanced stage, which includes patients with locally advanced (Stage III) disease whose cancer has spread to lymph nodes and other organs in the chest, and patients with metastatic (Stage IV) disease whose cancer has spread to other parts of the body (including the brain – see central nervous system metastases in NSCLC). In 2016, 70% of patients in England and Wales were diagnosed with advanced stage disease (20% and 50% for stages III and IV, respectively).[7] Due to late diagnosis, the prognosis for patients diagnosed with lung cancer is often poor, with only 5% of patients in the UK surviving for ten years or more.[10]

ROS1 positive NSCLC

In recent years, a number of molecular alterations have been identified in NSCLC, some of which are key oncogenic drivers. This has led to the development and approval of targeted therapies with specific tyrosine kinase inhibitor (TKI) activity including, epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors and ROS1 inhibitors.

The ROS1 gene was originally discovered as a homolog of the transforming sequence of the avian sarcoma ribonucleic acid (RNA) virus[11, 12] and encodes an orphan receptor tyrosine kinase (RTK) without a known ligand, whose physiological function is still unclear. ROS1 is an RTK that may potentially undergo genetic rearrangements in a variety of human cancers including glioblastoma, NSCLC and ovarian cancer. These rearrangements can create fusion proteins in which the kinase domain of ROS1 becomes constitutively active and drives cellular proliferation.[13] Known ROS1 fusion partners in lung cancer include FIG, SLC34A2, SDC4, and CD74 is the most frequently detected ROS1 fusion in this group of patients.[14]

ROS fusion proteins were first reported in NSCLC in 2007.[15] Since then, ROS1 fusions have become an established therapeutic target in lung cancer. However, ROS1 fusions are still rare and occur in 1-2% of patients with NSCLC, representing a lower frequency than several other known oncogenic drivers in NSCLC.[16-22] ROS1 fusions are found almost exclusively in non-squamous tumours, the majority being adenocarcinoma (80–100%).[16, 17, 20]

Among ROS1-positive NSCLC tumours, ROS1 fusions rarely overlap with ALK fusions or with oncogenic EGFR and Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations.[23] Therefore, ROS1 fusions define a unique molecular subset of oncogenic drivers in NSCLC. However, it should be noted that several of the predominant phenotypic clinicopathological characteristics associated with ROS1 fusions are shared with ALK fusions (e.g. younger age, non-smoker or light smoking, and adenocarcinoma histologic type).[16, 22]

As described above, ROS1-positive advanced NSCLC is very rare and therefore, there are limited data for the life expectancy of ROS1-positive NSCLC patients.

However, ROS1 fusions (along with ALK and neurotrophic tyrosine receptor kinase [NTRK] fusions) are thought to be associated with worsened prognosis in cancer.[24] In a recent study comprising of 103 ROS1-positive NSCLC patients not treated with ROS1 targeted therapy (the majority of patients [87%] received pemetrexed-based chemotherapy), the median progression-free survival (PFS) and overall survival (OS) were approximately 8 and 20 months, respectively.[25]

Symptoms of advanced NSCLC

The most common symptoms of advanced lung cancer are feeling tired and unwell. However, people with advanced lung cancer may also experience many other symptoms including persistent cough, breathlessness and ongoing chest infections.[26] People with metastatic disease may experience further symptoms relating to the site of metastases, for example, patients with brain metastases often experience confusion and headaches.[26]

These symptoms can significantly impact patient and carer health-related quality of life (HRQL). In a study assessing the association between advanced NSCLC patient clinical characteristics and patient and caregiver humanistic burden, there was an apparent trend for worsening EQ-5D-3L scores with declining Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). Scores ranged from a mean of 0.84 for patients with an ECOG Performance Status of 0 to 0.29 for those with an ECOG Performance Status of 3 or 4.[27] This deterioration is also reflected in increased caregiver burden, with 34% of caregivers of patients with advanced NSCLC and an ECOG PS of 0, reporting some or extreme problems with anxiety or depression, which increased to 66.7% of caregivers of patients with an ECOG-PS of 3 or 4 ($p=0.0150$).[27] Therefore, there is a need for interventions to maintain patients' physical function to relieve the humanistic burden of both patients and caregivers.

Central nervous system metastases in NSCLC

NSCLC has a high propensity to metastasise to the central nervous system (CNS). Among patients with NSCLC, between 10% to 25% of patients present with CNS metastases at the time of diagnosis and up to 50% will develop CNS metastases at some point during the course of their disease.[28-32] Due to the small ROS1-positive NSCLC patient population, limited data are available for the numbers of patients with

CNS metastases at the time of diagnosis. Furthermore, results from available studies are variable as CNS metastases incidence is reported in 19%–53% of patients with ROS1-positive NSCLC.[33-35]

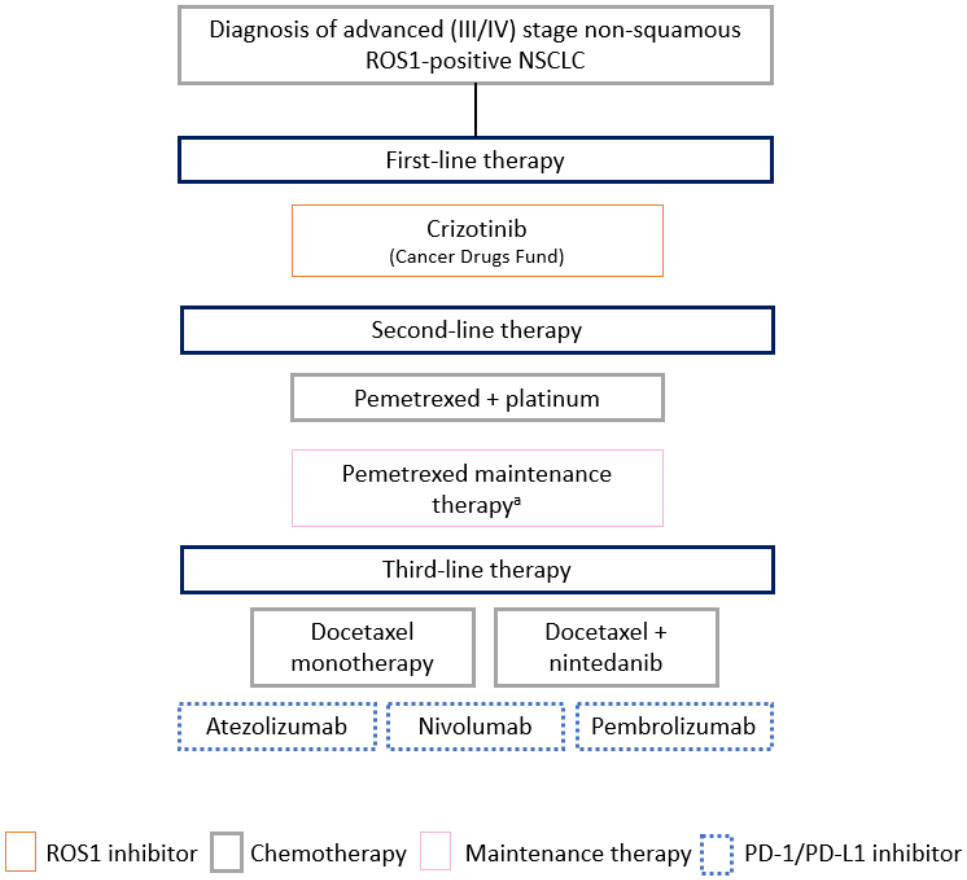
CNS metastases (including brain metastases) in advanced NSCLC are a major clinical issue and are associated with a significant reduction in quality of life and estimated life expectancy. In a real-world evidence study, estimated life expectancy was significantly shorter for NSCLC patients with brain metastases (25.3 weeks) compared with patients with metastases of the contralateral lung (50.5 weeks), bone (49.4 weeks), adrenal glands (48.7 weeks) and liver (44.9 weeks; all $p<0.01$).[36]

The symptoms of CNS metastases include drowsiness and confusion, severe headaches, often with sickness and weakness of an arm or leg.[26] These symptoms can significantly impact patient HRQL. Newly diagnosed advanced NSCLC patients with brain metastases experienced a significantly faster and clinically meaningful deterioration in 18 patient-reported outcome measures compared to patients without brain metastases. These 18 measures included all European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) apart from global health status, all of the Lung Cancer Module of the M.D. Anderson Symptom Inventory (MDASI-LC), and the Rotterdam Activity Level Scale (RALS; all $p<0.05$).[37]

Clinical pathway of care

The current clinical pathway of care for advanced ROS1-positive NSCLC patients in NHS England is depicted in Figure 1. This is based on the NICE pathway for the management of ROS1-positive NSCLC[1], but adapted in line with clinical consultation and the previous committee conclusions on relevant comparators in the ROS1-positive NSCLC setting (TA529) that confirm platinum-doublets are not commonly used to treat in patients with non-squamous histology where ROS1 arises most frequently.[3, 38]

Figure 1: Clinical pathway of care for advanced ROS1-positive NSCLC in NHS England



Key: NHS, National Health Service; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
Notes: [a], only recommended after pemetrexed + cisplatin.
Source: adapted from the NICE pathway for the management of advanced non-squamous (Stages IIIB and IV) NSCLC: ROS1-positive.[1]

In accordance with this pathway, patients with ROS1-positive non-squamous NSCLC should currently receive crizotinib as first line treatment.[1] Crizotinib is recommended for use within the CDF, only if the conditions in the managed access agreement are followed.[38] Crizotinib is considered standard of care for ROS1-positive NSCLC by the clinical community, and chemotherapy would not be used before crizotinib for any patients confirmed as ROS1-positive.[2, 3]

On progression after first line therapy, patients should be offered pemetrexed plus platinum-based chemotherapy as second-line therapy.[1] As noted above, although platinum-doublets are also included as second-line treatment options in the NICE

pathway, these are not commonly used to treat patients with ROS1-positive NSCLC in clinical practice.[3, 38]

If patients do not immediately progress after second-line therapy, those treated with pemetrexed plus cisplatin should be treated with pemetrexed maintenance therapy.[1] Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in adults when their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy, their ECOG performance status is 0 or 1 at the start of maintenance treatment and the company provides the drug according to the terms of the commercial access agreement as agreed with NHS England.[39] Up to 80% of patients are estimated to receive pemetrexed maintenance if they are fit enough to receive pemetrexed plus cisplatin in clinical practice.[3]

On progression after second-line therapy (first-line chemotherapy), recommended treatments include, docetaxel monotherapy, nintedanib with docetaxel, the programmed cell death protein 1 (PD-1) inhibitor nivolumab and the programmed death-ligand 1 (PD-L1) inhibitors atezolizumab and pembrolizumab.[1]

Entrectinib is intended for use in the first- or second-line setting but is expected to be used in the first-line setting (on confirmation of ROS1-positive status) in consideration of its clinical effectiveness (see Section B.2). Therefore, while the relevant comparators according to the clinical pathway of care are crizotinib and pemetrexed plus platinum, entrectinib would primarily be expected to displace crizotinib.

Unmet medical need

There is an unmet medical need for targeted treatment options that offer improved clinical effectiveness including extracranial and intracranial activity,[3] and improved tolerability at earlier lines of treatment for patients with ROS1 NSCLC, to delay the use of increasingly ineffective non-targeted options at later lines.

Crizotinib is currently the only targeted therapy licensed for use in advanced ROS1-positive NSCLC. However, crizotinib lacks proven CNS efficacy, which is important as approximately 19%–53% of patients with ROS1-positive NSCLC develop CNS

metastases.[33-35] As described previously, CNS metastases are a major clinical issue associated with various symptoms (e.g. drowsiness and confusion) that can significantly impact patient HRQL and life expectancy.[26, 37]

Non-targeted chemotherapy is the alternative treatment option at early lines. The toxic, systemic nature of chemotherapy has well accepted limitations with regard to potential side effects that can markedly impact patient quality of life.

B.1.4. Equality considerations

In the technology appraisal of crizotinib for treating ROS1-positive advanced NSCLC (TA529), there were concerns of inequitable access to ROS1-targeted treatments due to regional variations in ROS1 testing.[38] As part of the access arrangements, it was therefore agreed that ROS1 testing should become a standard part of diagnostic work-up, and ROS1 testing is included in the 2019/2020 National Genomic Test Directory for Cancer.[4] As such, this equality consideration should no longer be a concern in future clinical practice.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

No published evidence for entrectinib in ROS1-positive NSCLC was identified. The regulatory evidence supporting this appraisal is presented from Section B.2.2.

Published evidence for crizotinib in ROS1-positive NSCLC was identified and is used to inform an indirect treatment comparison (ITC) presented in Section B.2.9. No published evidence for chemotherapy in ROS1-positive NSCLC was identified. Searches were therefore extended to ALK-positive NSCLC and evidence from this group is used to inform further ITCs presented in Section B.2.9.

B.2.2. List of relevant clinical effectiveness evidence

The regulatory evidence to support entrectinib in ROS1 positive NSCLC, and the focus of this submission, is the clinical development program for entrectinib ROS1-

positive NSCLC, which consists of three clinical studies in adult patients with solid tumours: ALKA-372-001, RXDX-101-01, and RXDX-101-02 (hereafter referred to as ALKA, STARTRK-1, and STARTRK-2, respectively).

A ROS1-positive NSCLC integrated analysis of efficacy was conducted across the three studies, based on the ROS1 positive primary efficacy set, which consists of adult patients with ROS1-positive NSCLC with measurable disease at baseline and at least 12 months follow-up from the time of first response. See Section B.2.4 for further details of the analysis populations. Because of the rare disease setting for ROS1-positive NSCLC, both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) agreed with the proposal to pool safety and efficacy data from the clinical studies.

The clinical development programme of entrectinib also includes Study RXDX-101-03 (STARTRK-NG), which is investigating the efficacy and safety of entrectinib in paediatric patients (children, adolescents and young adults) with recurrent or refractory solid tumours and primary CNS tumours, with or without tropomyosin receptor kinase (TRK), ROS1, or ALK fusions. No ROS1-positive patients are enrolled in this trial to date and therefore it was not included in the integrated efficacy analyses supporting this indication or the evidence synthesis including the economic modelling included in this appraisal. It is included in an integrated safety analyses of all patients treated across the clinical development programme, which is presented alongside the ROS1 safety population in Section B.2.10.

Summaries of the ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG studies are presented in Table 3. Further details of the design of ALKA, STARTRK-1 and STARTRK-2 are provided in Section B.2.3.

Table 3: Clinical effectiveness evidence – ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG

Study	**ALKA-372-001 (ALKA)**					**RXDX-101-01 (STARTRK-1)**					**RXDX-101-02 (STARTRK-2)**					**RXDX-101-03 (STARTRK-NG)**				
Study design	ALKA is an ongoing, Phase I, single-arm, first-in-human, multicentre, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme					STARTRK-1 is an ongoing, Phase I, single-arm, multicentre, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme					STARTRK-2 is an ongoing, Phase II, global, single-arm, registration-enabling, multicentre, basket study					STARTRK-NG is an ongoing, Phase I/II, open-label, dose-escalation and expansion study				
Population	Patients (≥18 years old) with advanced or metastatic solid tumours with TRKA/B/C, ROS1, or ALK molecular alterations					Patients (≥18 years old) with solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations					Patients (≥18 years old) with advanced or metastatic solid tumours with NTRK1/2/3, ROS1, or ALK gene fusion (excluding ALK-positive NSCLC)					Patients (2-21 years old) with relapsed or refractory extracranial solid tumours (Phase 1), with additional expansion cohorts (Phase Ib) in patients with primary brain tumours harbouring TRK, ROS1, or ALK gene fusions, neuroblastoma, and other non-neuroblastoma, extracranial solid tumours harbouring TRK, ROS1, or ALK gene fusions				
Intervention	Entrectinib (n=58)					Entrectinib (n=76)					Entrectinib (n=207)					Entrectinib (n=16)				
Comparator	N/A					N/A					N/A					N/A				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes		**Indicate if trial used in the economic model**	Yes	
	No			No		No			No		No			No		No	✓		No	✓

Study	ALKA-372-001 (ALKA)	RXDX-101-01 (STARTRK-1)	RXDX-101-02 (STARTRK-2)	RXDX-101-03 (STARTRK-NG)
Rationale for use/non-use in the model	ALKA presents clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	STARTRK-1 presents clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	STARTRK-2 presents clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	STARTRK-NG does not present clinical evidence in support of entrectinib in the population directly relevant to the decision problem.
Reported outcomes specified in the decision problem	• Objective Response Rate • Duration of Response • **Progression-free Survival** • **Overall Survival** • **Time to treatment discontinuation** • **Adverse effects of treatment**	• Objective Response Rate • Duration of Response • **Progression-free Survival** • **Overall Survival** • **Time to treatment discontinuation** • **Adverse effects of treatment**	• Objective Response Rate • Duration of Response • **Progression-free Survival** • **Overall Survival** • **Time to treatment discontinuation** • **Adverse effects of treatment** • **Health-related quality of life**	• Objective Response Rate • **Progression-free Survival** • **Overall Survival** • **Adverse effects of treatment**
All other reported outcomes	• Disease Control • Dose-Limiting Toxicity • Maximum Tolerated Dose • Recommended Phase 2 Dose • Plasma Concentrations of Entrectinib	• Disease Control • Dose-Limiting Toxicity • Maximum Tolerated Dose • Recommended Phase 2 Dose • Plasma Concentrations of Entrectinib	• Time to Response • Clinical Benefit Rate • Intracranial Tumour Response • CNS Progression-free Survival	• Dose-Limiting Toxicity • Maximum Tolerated Dose • Recommended Phase 2 Dose • Plasma Concentrations of Entrectinib
Key: ALK, anaplastic lymphoma kinase; CNS, central nervous system; N/A, not applicable; NSCLC, non-small cell lung cancer.				

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

Clinical development program for entrectinib in ROS1-positive NSCLC

Study design for the three entrectinib studies

Entrectinib was initially investigated as a single agent in the first-in-human study, ALKA – conducted exclusively in Italy, and subsequently STARTRK-1 – conducted in the US and South Korea. ALKA and STARTRK-1 are both Phase I, single-arm, open-label studies of oral entrectinib in patients with locally advanced or metastatic solid tumours with NTRK, ROS1, or ALK molecular alterations and who had received any prior therapy. During dose escalation, patients were enrolled into cohorts using a "3+3" scheme until selection of the recommended Phase II dose (RP2D; 600mg/day in 28-day cycles).

Following determination of the RP2D, and early evidence of clinical activity observed with entrectinib in the Phase I studies, the entrectinib clinical development program was expanded with the initiation of STARTRK-2. STARTRK-2 is a Phase II, global, single-arm, open-label, multicentre basket study of oral entrectinib at the RP2D in patients with solid tumours with NTRK, ROS1, or ALK gene fusions. Patients were enrolled across multiple solid tumour "baskets" that were planned to be individually analysed as separate cohorts, including "non-evaluable" baskets intended to provide broader access to entrectinib treatment.

A summary of the methodology of the three studies that form the basis of the integrated analyses supporting the ROS1-positive advanced NSCLC indication is provided in Table 4 and full details are presented in Appendix L.1.

Table 4: Summary of the methodology of ALKA, STARTRK-1 and STARTRK-2

Trial number (acronym)	EudraCT 2012-000148-88 (ALKA)	NCT02097810 (STARTRK-1)	NCT02568267 (STARTRK-2)
Location	2 centres in Italy	11 centres in 3 countries: the US, South Korea and Spain	84 centres in 15 countries across 4 continents: Australia, Europe (including the UK), Asia and North America (the US)
Trial design	Phase I, dose escalation study of oral entrectinib in adult patients with advanced/ metastatic solid tumours with TRKA/B/C, ROS1, or ALK genetic alterations.	Phase I, dose escalation and open-label study of oral entrectinib in adult patients with locally advanced or metastatic cancer confirmed to be positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK gene fusion.	Phase II, open-label study of oral entrectinib for the treatment of patients with solid tumours that harbour an NTRK1/2/3, ROS1, or ALK gene fusion.
Key eligibility criteria	• Adult patients with advanced/ metastatic solid tumours with TRKA, TRKB, TRKC, ROS1, or ALK genetic alterations – Including those with controlled asymptomatic CNS • No effective standard therapy available, suitable or accepted as an alternative to trial enrolment • No previous targeted treatment for genetic alterations but other prior cancer therapy allowed • ECOG performance status ≤2 • No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis • Not enrolled in another therapeutic study	• Adult patients with advanced/ metastatic solid tumours – With NTRK, ROS1, ALK or other genetic alterations of interest for dose expansion segment – Including those with controlled asymptomatic CNS • No effective standard therapy available, suitable or accepted as an alternative to trial enrolment • Previous TKI inhibitor treatment for NTRK gene arrangements in patients with NTRK mutant disease • Prior cancer therapy including previous targeted treatment	• Adult patients with advanced/ metastatic solid tumours with NTRK, ROS1, or ALK genetic alterations – Including those with controlled asymptomatic CNS • No previous targeted treatment for genetic alterations but other prior cancer therapy allowed • ECOG performance status ≤2 • No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis • No peripheral neuropathy Grade ≥2 or history of TKI-induced pneumonitis • Not enrolled in another therapeutic study

Trial number (acronym)	EudraCT 2012-000148-88 (ALKA)	NCT02097810 (STARTRK-1)	NCT02568267 (STARTRK-2)
		allowed, with the exception of prior entrectinib • ECOG performance status ≤2 • No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis • No peripheral neuropathy Grade ≥2 or history of TKI-induced pneumonitis • Not enrolled in another therapeutic study	
Trial drugs	Entrectinib 100mg/m^2 to 1600mg/m^2 given orally according to varying schedules	**Dose escalation segment:** Entrectinib 100mg/m^2 given orally once daily and escalated in a conventional "3+3" scheme up to MTD **Dose expansion segment:** Entrectinib 600mg given orally (as three 200mg capsules) once daily	Entrectinib 600mg given orally (as three 200mg capsules) once daily
Primary outcomes (including scoring methods and timings of assessments)	To determine first cycle DLTs and MTD	**Dose escalation segment:** To determine first cycle DLTs, MTD, and the RP2D **Dose expansion segment:** ORR, defined as the proportion of patients with a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator	ORR, defined as the proportion of patients with a confirmed CR or PR according to RECIST v1.1 as assessed by BICR

Trial number (acronym)	EudraCT 2012-000148-88 (ALKA)	NCT02097810 (STARTRK-1)	NCT02568267 (STARTRK-2)
Other outcomes used in the economic model/specified in the scope	• ORR, defined as the proportion of patients with a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator • Safety Of note, DOR, PFS, and OS were not efficacy endpoints of this study; however, individual evaluations and summary statistics for overall treated and evaluable patients were planned as exploratory analyses.	**Dose escalation segment:** • ORR, defined as the proportion of patients with a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator **Dose escalation & expansion segment:** • CBR, defined as the proportion of patients with a confirmed CR, PR, or stable disease for >6 months • DOR, defined as the time from the first date of objective response (either CR or PR) until the date of PD or death • PFS, defined as the time from first dose of entrectinib to tumour progression or death due to any cause • OS, defined as the time from first dose of entrectinib to death due to any cause • Safety **Dose expansion segment:** • Intracranial tumour response in patients with CNS disease according to RANO or RANO-BM as applicable as assessed by BICR	• BOR, defined as the best radiological response recorded from the start of treatment until disease progression • CBR, defined as the proportion of patients with a confirmed CR, PR or stable disease for >6 months • DOR, defined as the time from the first date of objective response (either CR or PR) until the date of PD or death • TTR, defined as the time from first dose of entrectinib to first documentation of objective response • PFS, defined as the time from first dose of entrectinib to tumour progression or death due to any cause • OS, defined as the time from first dose of entrectinib to death due to any cause • Intracranial tumour response in patients with brain metastases at baseline according to CNS RECIST as assessed by BICR • Time to CNS progression, defined as time from first dose of entrectinib to first documentation of radiographic CNS disease

Trial number (acronym)	EudraCT 2012-000148-88 (ALKA)	NCT02097810 (STARTRK-1)	NCT02568267 (STARTRK-2)
			progression or death due to any cause • Intracranial PFS, defined as time from first dose of entrectinib to CNS tumour progression or death due to any cause • Safety • HRQL as measured by EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D

Key: BICR, Blinded Independent Central Review; BOR, best overall response; CBR, clinical benefit rate; CNS, central nervous system; CR, complete response; DLTs, dose-limiting toxicities; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and Lung Cancer Module; EQ-5D, EuroQol-5 Dimension; GI, gastrointestinal; HRQL, health-related quality of life; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO; Radiographic Assessment in Neuro-oncology; RANO-BM, Radiographic Assessment in Neuro-oncology- Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor; TTR, Time to response.
Source: ALKA CSR;[40] STARTRK-1 CSR;[41] STARTRK-2 CSR.[42]

ROS1 testing

The molecular characterisation of tumour tissue was evaluated by several different assay methods prior to study enrolment in individual studies, including immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH), reverse transcription-polymerase chain reaction, and next generation sequencing.

Only those harbouring gene fusions in ROS1 that were detected by a nucleic acid-based diagnostic method and predicted to translate into a fusion protein with a functional kinase domain were considered to have a positive gene fusion status and included in the ROS1-positive integrated analyses. Where possible, patient samples that were determined to be ROS1-positive by local testing, were re-tested centrally by the Sponsor.

Endpoints in the integrated analysis

The primary endpoints of objective response rate (ORR) (including best overall response [BOR]) and duration of response (DoR) were considered appropriate endpoints for the integrated analysis of efficacy across the three entrectinib studies. These endpoints were based on the Phase II STARTRK-2 study endpoints. Although the primary objectives of ALKA and STARTRK-1 were safety-based, one of the key secondary endpoints in both studies was the determination of ORR, which is similar to the primary objective of the Phase II study STARTRK-2.

The ROS1-positive NSCLC integrated analysis of efficacy was based on blinded independent committee review (BICR) determinations of ORR using RECIST v1.1. Tumour scans for patients in the STARTRK-2 study were evaluated in a prospective manner. Tumour scans for selected patients (those included in the efficacy-evaluable patient populations) from the STARTRK-1 and ALKA studies were evaluated by the same BICR team as STARTRK-2 using equivalent Imaging Review Charters but performed in a retrospective manner. Sensitivity analyses based on investigator assessed (IA) ORR and DoR were also conducted to evaluate the robustness of therapeutic efficacy.

Other clinically meaningful endpoints including OS and PFS were evaluated as secondary endpoints. Sensitivity analyses were also performed for PFS to evaluate

the impact of BICR assessment and the impact of censored patients on results (missing tumour assessment and for new non-protocol anti-cancer therapy).

The presence of CNS metastases at baseline was determined by the investigator for subgroup analyses. Additional endpoints assessed in patients with CNS metastases at baseline confirmed by BICR were intracranial Objective Response Rate (IC-ORR), Intracranial-Duration of Response (IC-DoR) and Intracranial PFS (IC-PFS).

Patient reported outcome (PRO) measures were only assessed in the STARTRK-2 study. The EORTC quality of life instruments and the EQ-5D instruments were used. Data were collected prior to any dosing of entrectinib or clinical activity on Day 1 of each visit starting at Cycle 1 and at the end of treatment. Further details of the PRO measures are provided in Appendix L.2. Trial endpoints and their relevance are discussed further in Section B.2.13.

Baseline demographics

Baseline characteristics of ROS1 positive NSCLC patients from ALKA, STARTRK-1, and STARTRK-2, who were included in the primary efficacy set are presented in Table 5.

The median age of patients in the primary efficacy set was 53.0 years (range: 46.0, 61.0), 64.2% of patients were female, just over half were non-smokers (58.5%) and the majority of patients had adenocarcinoma histology (76.1%). The most frequently represented gene fusion partner was CD74-ROS1 (39.6%), whereas, each of the other fusion partners were reported in ≤13.2% of patients.

The ROS1 positive NSCLC primary efficacy set included both treatment naïve and pre-treated patients. 17 (32.1%) patients had never received systemic advanced/metastatic treatments and were therefore receiving entrectinib as a first-line therapy. Most patients (94.3%) presented with metastatic disease at baseline, of which the most common sites were the lung (71.7%) and the lymph nodes (71.7%). 23 patients (43.4%) had documented baseline CNS metastases as assessed by investigator. Overall, 15 patients (28.3%) had received prior radiotherapy of the brain.

Table 5: Baseline characteristics from ALKA, STARTRK-1, and STARTRK-2 and the overall primary efficacy set

	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (primary efficacy set) (n=53)
Age (years)				
Mean (SD)	53.0	55.4	53.3	53.5
Median (range)	52.0 (46.0, 63.0)	57.0 (50.0, 60.0)	53.0 (46.0, 61.0)	53.0 (46.0, 61.0)
Age categories (years), n (%)				
<65	7 (77.8)	6 (85.7)	29 (78.4)	42 (79.2)
≥65	2 (22.2)	1 (14.3)	8 (21.6)	11 (20.8)
Sex, n (%)				
Male	2 (22.2)	3 (42.9)	14 (37.8)	19 (35.8)
Female	7 (77.8)	4 (57.1)	23 (62.2)	34 (64.2)
Race, n (%)				
White	8 (88.9)	3 (42.9)	20 (54.1)	31 (58.5)
Asian	1 (11.1)	4 (57.1)	14 (37.8)	19 (35.8)
Black or African American	0	0	3 (8.1)	3 (5.7)
ECOG Score, n (%)				
0	3 (33.3)	2 (28.6)	15 (40.5)	20 (37.7)
1	6 (66.7)	4 (57.1)	17 (45.9)	27 (50.9)
2	0	1 (14.3)	5 (13.5)	6 (11.3)
History of smoking, n (%)				
No	6 (66.7)	6 (85.7)	19 (51.4)	31 (58.5)
Yes	3 (33.3)	1 (14.3)	18 (48.6)	22 (41.5)

	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (primary efficacy set) (n=53)
Histology, n (%)				
Adenocarcinoma	0	0	35 (94.6)	35 (76.1)
Bronchioloalveolar carcinoma	0	0	1 (2.7)	1 (2.2)
Cytological	2 (22.2)	0	0	2 (4.3)
Histological	7 (77.8)	0	0	7 (15.2)
Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements	0	0	1 (2.7)	1 (2.2)
Time since diagnosis (months)				
Mean	NE	22.2	20.8	21.0
Median (range)	NE	20.3 (1.0, 39.5)	11.0 (4.0, 23.1)	11.5 (3.3, 28.9)
Stage at initial diagnosis, n (%)				
IB	0	0	2 (5.4)	2 (4.5)
IIB	0	1 (14.3)	1 (2.7)	2 (4.5)
III	0	3 (42.9)	0	3 (6.8)
IIIA	0	0	5 (13.5)	5 (11.4)
IIIB	0	0	3 (8.1)	3 (6.3)
IIIC	0	0	1 (2.7)	1 (2.3)
IV	0	3 (42.9)	24 (64.9)	27 (61.4)
Unknown	0	0	1 (2.7)	1 (2.3)
Extent of disease, n (%)				
Localised	1 (11.1)	0	0	1 (1.9)
Locally advanced	1 (11.1)	0	1 (2.7)	2 (3.8)
Metastatic disease	7 (77.8)	7 (100.0)	36 (97.3)	50 (94.3)

	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (primary efficacy set) (n=53)
Metastatic sites[a], n (%)				
Bone	1 (11.1)	3 (42.9)	16 (43.2)	20 (37.7)
Brain	2 (22.2)	3 (42.9)	18 (48.6)	23 (43.4)
Liver	0	0	8 (21.6)	8 (15.1)
Lung	9 (100.0)	6 (85.7)	23 (62.2)	38 (71.7)
Lymph nodes	7 (77.8)	4 (57.1)	27 (73.0)	38 (71.7)
Other	5 (55.6)	1 (14.3)	10 (27.0)	16 (30.2)
NSCLC Gene fusion partner, n (%)				
CD74 – ROS1	1 (11.1)	1 (14.3)	19 (51.4)	21 (39.6)
EZR – ROS1	1 (11.1)	0	4 (10.8)	5 (9.4)
SDC4 – ROS1	1 (11.1)	0	5 (13.5)	6 (11.3)
SLC34A2 – ROS1	0	0	7 (18.9)	7 (13.2)
TPM3 – ROS1	0	0	2 (5.4)	2 (3.8)
Unknown	6 (66.7)	6 (85.7)	0	12 (22.6)
Baseline CNS lesions by investigator[b], n (%)				
Measurable	1 (11.1)	0	4 (10.8)	5 (9.4)
Present	1 (11.1)	3 (42.9)	14 (37.8)	18 (34.0)
Absent	7 (77.8)	4 (57.1)	19 (51.4)	30 (56.6)
Any prior radiotherapy of the brain, n (%)				
Yes	2 (22.2)	3 (42.9)	10 (27.0)	15 (28.3)
No	7 (77.8)	4 (57.1)	27 (73.0)	38 (71.7)
Time from end of prior radiotherapy to first dose, n (%)				
<2 months	1 (50.0)	3 (100.0)	5 (50.0)	9 (60.0)

	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (primary efficacy set) (n=53)
2 to <6 months	0	0	2 (20.0)	2 (13.3)
≥6 months	1 (50.0)	0	3 (30.0)	4 (26.7)
Prior CNS disease treatment, n (%)	2 (22.2)	3 (42.9)	3 (8.1)	8 (15.1)
Stereotactic Radiotherapy	0	3 (42.9)	0	3 (5.7)
Whole Brain +/- Stereotactic Radiotherapy	2 (22.2)	0	3 (8.1)	5 (9.4)
Previous therapy, n (%)	9 (100.0)	5 (71.4)	32 (86.5)	46 (86.8)
Any chemotherapy	9 (100.0)	4 (57.1)	29 (78.4)	42 (79.2)
Any immunotherapy	0	0	5 (13.5)	5 (9.4)
Any targeted therapy	2 (22.2)	1 (14.3)	6 (16.2)	9 (17.0)
Any hormonal therapy	0	0	1 (2.7)	1 (1.9)
Number of prior systemic therapies,[c] n (%)				
0	0	3 (42.9)	14 (37.8)	17 (32.1)
1	4 (44.4)	3 (42.9)	16 (43.2)	23 (43.4)
2	3 (33.3)	0	2 (5.4)	5 (9.4)
≥3	2 (22.2)	1 (14.3)	5 (13.6)	8 (15.1)
Any previous radiotherapy, n (%)	3 (33.3)	3 (42.9)	18 (48.6)	24 (45.3)
Any previous surgeries, n (%)	2 (22.2)	5 (71.4)	20 (54.1)	27 (50.9)

Key: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NE, not estimable; NSCLC, non-small cell lung cancer; SD, standard deviation.
Notes: [a], Patients may have multiple sites of metastases at baseline; [b], Patients with history of CNS disease include those having prior surgery and/or radiation to the CNS, but not presenting with CNS lesions at baseline per the RECIST 1.1 Investigator assessment; [c], the definition of lines of therapy excluded (neo)-adjuvant and maintenance therapy. As a result, some patients that received chemotherapy were classified as having no previous lines of treatment.
Source: Summary of clinical efficacy.[43]

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

As described in Section B.2.2, data from the following three clinical studies in adult patients with solid tumours have been pooled and analysed collectively: ALKA, STARTRK-1, and STARTRK-2. The hypothesis and associated statistical analysis methods adopted for the integrated efficacy analyses in the ROS1-positive advanced NSCLC patient population are tabulated in Table 6.

See Appendix D.2 for full details of the number of participants eligible to enter the entrectinib ROS1-positive clinical trial programme and the CONSORT Flow Diagram for patient disposition.

Analysis populations

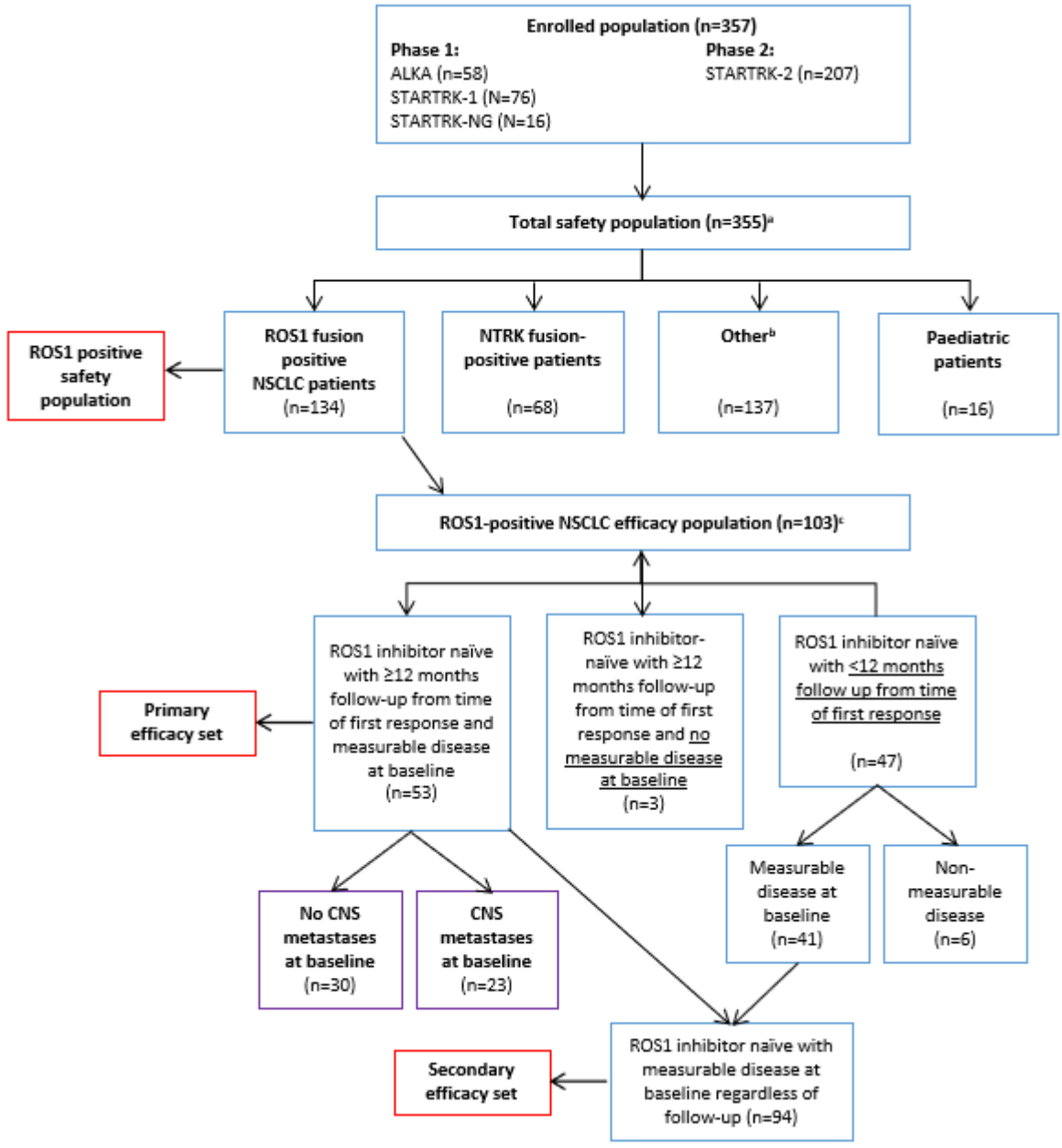
The following analysis populations were used in the integrated analysis of the entrectinib ROS1-positive NSCLC data:

- **Primary efficacy set:** The primary efficacy set consisted of ROS1-positive, ROS1 inhibitor naive NSCLC patients with measurable disease at baseline (as per RECIST v1.1) and ≥12 months follow-up from onset of response or treatment discontinuation at the time of the clinical cut-off date (CCOD; 31 May 2018)
- **Secondary efficacy set:** The secondary efficacy set consisted of the primary efficacy set plus ROS1-positive, ROS1 inhibitor naïve NSCLC patients with measurable disease at baseline and <12 months follow-up
- **ROS1 safety population:** The ROS1 safety population consisted of all ROS1-positive NSCLC patients who received at least one dose of entrectinib
- **Total safety population:** The total safety population consisted of all patients treated with entrectinib across the clinical trial programme including STARTRK-NG as well as ALKA, STARTRK-1 and STARTRK-2

As described in Section B.2.3, the presence of CNS disease at baseline was determined by the investigator. These results were used to split the primary efficacy set into two important subpopulations: patients with CNS metastases at baseline and patients without CNS metastases at baseline. Other pre-specified subgroup analyses are detailed below.

Figure 2 presents the total number of patients enrolled in the three studies used in the ROS1-positive integrated analysis and in each of the different ROS1-positive NSCLC analysis populations.

Figure 2: Patient populations and analysis sets



Key: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer.
Notes: [a], excludes patients who did not receive entrectinib (n=2); [b], includes ROS1-positive non-NSCLC, ALK fusion-positive and no gene fusion patients; [c], excludes patients who received prior ROS1 inhibitor (n=27), ECOG PS>2 (n=3) and ROS1 biomarker ineligibility (n=1).
Source: Statistical analysis plan ROS1-positive NSCLC;[44] Summary of clinical efficacy.[43]

Integrated efficacy analysis

In accordance with the statistical analysis plan for the entrectinib ROS1-positive NSCLC integrated analysis, the analysis for marketing application submission was to be performed after approximately 50 ROS1-positive NSCLC patients had been enrolled across the Phase I and Phase II studies. All patients were to have at least 12 months of efficacy follow-up from the time of response, or will have discontinued study treatment at the time of the CCOD.[44] The target number of patients was achieved as of the 31 May 2018 (CCOD) and the database was locked for the primary integrated efficacy analysis on 31 July 2018.[43]

Data presented for the primary integrated efficacy analysis are from this database lock and include all data up to and including the 31 May 2018. At this time, the primary efficacy set included 53 patients. As described in Section B.2.3, the primary integrated analysis of efficacy was based on BICR determinations of ORR using RECIST v1.1. Formal significance tests were not performed, and p-values were not reported. Instead, point estimates with 95% 2-sided confidence intervals (CI) were utilised to estimate magnitude of effects. Analyses of secondary endpoints occurred alongside the primary integrated efficacy analysis. However, at the time of the database lock for the primary integrated efficacy analysis (31 May 2018), data for OS were immature and heavily censored (>80%), therefore, only an interim OS analysis was available.

A further analysis was conducted at the request of the FDA at Day 75 based on a CCOD of 30 October 2018 for which the database lock was 21 December 2018.[45] Analyses of the primary endpoints (ORR and DoR), clinical benefit rate (CBR), PFS and OS endpoints were conducted on this second data cut. At the time of the database lock for the updated integrated efficacy analysis (21 December 2018), data for OS were still immature and heavily censored (>75%), therefore, similar to the primary integrated efficacy analysis, only an interim OS analysis was available.[45]

Subgroup analyses

Prespecified subgroup analyses were planned for the primary integrated analysis for several baseline demographic and disease characteristics, where patient numbers allowed (n≥5) (see Appendix E).

Table 6: Summary of statistical analyses of the primary integrated efficacy analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
• EudraCT 2012-000148-88 (ALKA) • NCT02097810 (STARTRK-1) • NCT02568267 (STARTRK-2)	The primary hypothesis objective was to the determine the response rate in ROS1-positive NSCLC patients treated with entrectinib	The primary integrated efficacy analysis was performed after 53 patients with ROS1-positive NSCLC in studies ALKA, STARTRK-1, and STARTRK-2 who had measurable disease at baseline had at least 12 months of efficacy follow-up from the time of first response for all responding patients, or had discontinued study treatment at the time of the CCOD (31 May 2018). Formal significance tests were not performed; therefore, P values are not be reported. Instead, 95% 2-sided CIs for point estimates will be utilised to estimate magnitude of effects. Because of the rarity of this patient population and the expectation of significant clinical benefit, no statistical adjustment was made to address the sources of multiplicity associated with this integrated analysis. No other statistical adjustments will be made to account for subgroup effects associated with pooling of data for this analysis.	Assuming the true ORR by BICR (ORR-BICR) is 70%, a sample size of at least 50 patients will yield a 95% 2-sided confidence interval (CI) with precision ±17% that will exclude a lower limit of 50%. A response rate that excludes 50% or higher is considered clinically meaningful.	Patients without a post-baseline tumour assessment were classed as non-responders in ORR and BOR analyses. Patients without documented disease progression or death were censored at the last tumour assessment date for DOR. The same censoring approach was applied to PFS but patients without a post-baseline tumour assessment were censored at the time of first entrectinib dose. Patients alive at the time of analysis or lost to follow-up / withdrew consent for further follow-up were censored on the last date they were known to be alive for OS; patients with no post-baseline information were censored at the time of first entrectinib dose.

Key: BICR, blinded independent central review; CCOD, clinical cut-off date; CI, confidence interval; CNS, central nervous system; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate.
Source: Statistical analysis plan ROS1-positive NSCLC;[44] Summary of clinical efficacy.[43]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The study design for the entrectinib ROS1-positive NSCLC integrated analyses was assessed using the Downs and Black checklist, which has been recommended as being suitable for use in systematic reviews that include non-randomised studies.[46]

The full details of the quality assessment can be found in Appendix D.3, but there was an overall low risk of bias in the context of the single-arm and pooled nature of the integrated analyses.

To minimise detection bias and to ensure reliability and consistency across datasets, BICR for the three studies was performed by the same third-party vendor, using the same group of independent readers and equivalent Imaging Charters (Section B.2.3). Because of the rare disease setting for ROS1-positive NSCLC, both the FDA and EMA agreed with the proposal to conduct a Phase II single-arm trial to enable registration, and to pool safety and efficacy data from earlier Phase I trials with data from this Phase II trial.

B.2.6. Clinical effectiveness results of the relevant trials

Primary endpoints – Response and duration of response

Entrectinib treatment demonstrated a clinically meaningful and durable systemic response in the primary efficacy set (Table 7). At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), the ORR as assessed by the BICR, was [redacted]% (95% CI: [redacted] to [redacted]), with [redacted]% of patients achieving complete response (CR) and [redacted]% of patients achieving partial response (PR). The median DoR follow-up from the time of first response was [redacted] months (95% CI: [redacted], [redacted]) in the primary efficacy set. Median DoR among responders, as assessed by the BICR, was [redacted] months (95% CI: [redacted] to [redacted]).

At the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), results for ORR and DoR as assessed by BICR were similar to those observed in the primary integrated efficacy analysis (Table 7), but [redacted] more [redacted] achieved a response and a higher proportion of patients ([redacted]%) achieved CR. Figure 3a and

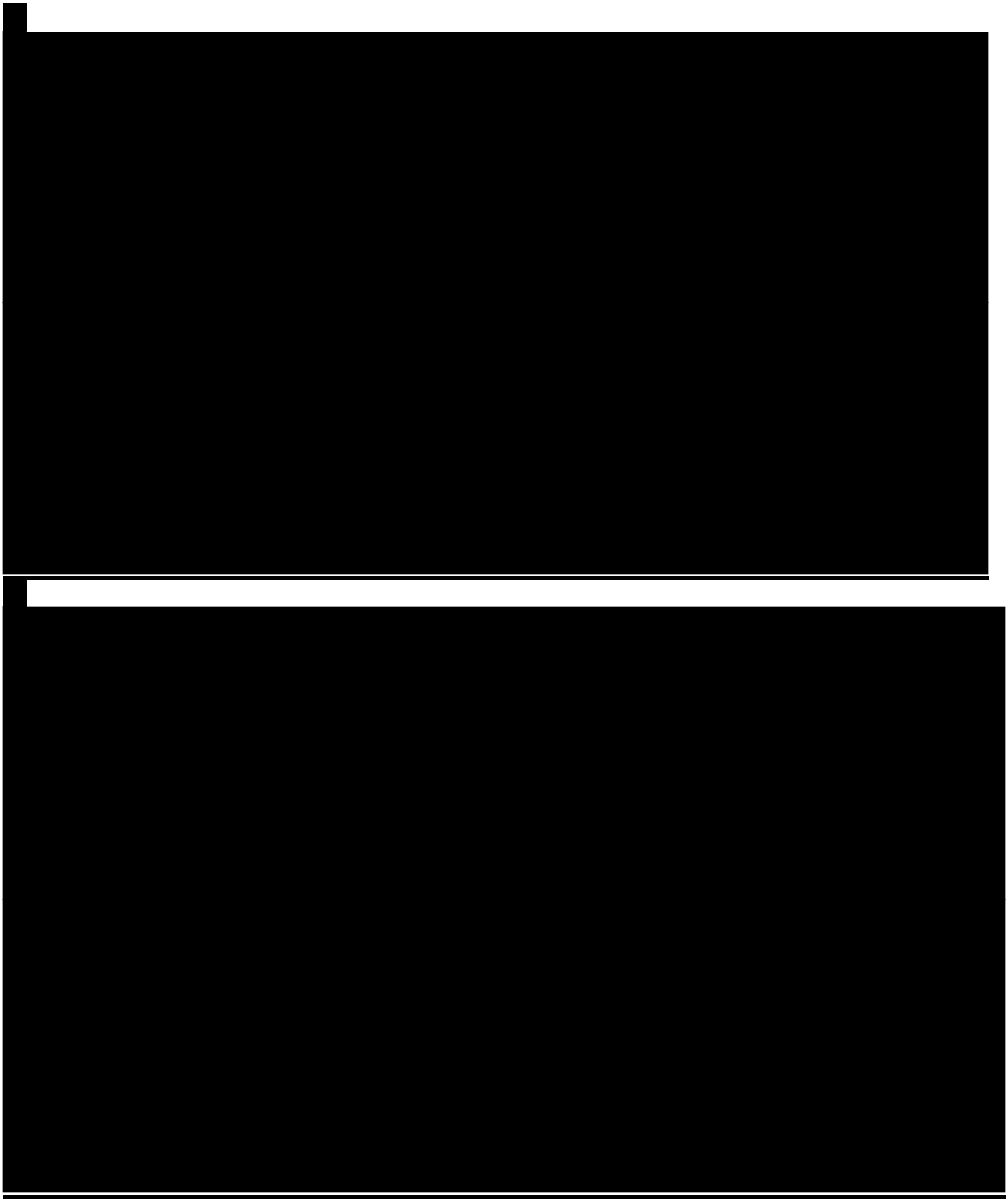
Figure 3b present the Kaplan–Meier (KM) curves for the DoR from the primary and the updated integrated efficacy analysis, respectively.

Table 7: Summary of response rate and duration of response (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	**STARTRK-1 (n=7)**	**STARTRK-2 (n=37)**	**Overall (n=53)**	**Overall (n=53)**
Objective response[a]					
Patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best objective response rate[b], n (%)					
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/PD[cd]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing or unevaluable[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of response[f]					
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; PD, progressed disease; PR, partial response; SD, stable disease.
Notes: [a], Objective response is defined as PR or CR confirmed by repeat-imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder; [b], Best Overall Response is derived per RECIST 1.1; [c], SD and Non-CR/Non-PD must be observed study day 35 or later, otherwise they count as NE; [d], Patients were categorised as having Non CR/PD if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator; [e], Missing or unevaluable category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response; [f], Median DOR was estimated using KM methods and measures of time from first response to death or progressive disease (censored at the last tumour assessment); CIs are calculated using the Clopper-Pearson method.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Figure 3: Duration of response (BICR Assessment) – Primary efficacy set



Key: BICR, blinded independent central review; CCOD, clinical cut-off date; DBL, database lock; NSCLC, non-small cell lung cancer.
Notes: [a], primary integrated efficacy analysis, which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 31 May 2018 - DBL 31 July 2018; [b], updated integrated efficacy analysis which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 30 October 2018 - DBL 21 December 2018.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Results from the sensitivity analyses of investigator assessed (IA) response rate in the primary efficacy set, were consistent with the results from the primary analysis,

demonstrating robustness of the data. Further details of the sensitivity analyses, including results, are presented in Appendix L.3.

Entrectinib treatment also resulted in a clinically meaningful and durable systemic response in the secondary efficacy set. The ORR and DoR for the secondary efficacy set were consistent with results from the primary efficacy set. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), the ORR as assessed by the BICR, was [redacted]% (95% CI: [redacted] to [redacted]), with [redacted]% of patients achieving CR and [redacted]% of patients achieving PR. Median DoR among responders, as assessed by the BICR, was [redacted] months (95% CI: [redacted] to [redacted]). Full details of the secondary efficacy set analyses are presented in Appendix L.4.

Secondary endpoints

Clinical benefit rate

At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), [redacted] patients in the primary efficacy analysis set had confirmed CR or PR, and [redacted] patients were observed to have durable SD for at least 6 months after the start of entrectinib, resulting in a CBR as assessed by the BICR, of [redacted]% (Table 8).

At the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), the CBR was similar to those observed in the primary integrated efficacy analysis (Table 8), but [redacted] more [redacted] achieved a response (as noted above).

Table 8: Clinical benefit rate (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (n=53)	Overall (n=53)
Clinical benefit rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.
Notes: Clinical benefit rate includes all patients with CR or PR plus patients with SD for at least 6 months after start of entrectinib. Otherwise, the patient is considered to not have clinical benefit; CI are calculated using the Clopper-Pearson method.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Progression-free survival

Systemic PFS observed in patients treated with entrectinib in the primary efficacy set was meaningfully durable (Table 9). At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), the median PFS in the primary efficacy set as assessed by the BICR, was [redacted] months (95% CI: [redacted] to [redacted]).

At the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), the median PFS was similar to that observed in the primary analysis (Table 9). Figure 4a and Figure 4b present the KM curves for PFS from the primary and the updated integrated efficacy analysis, respectively.

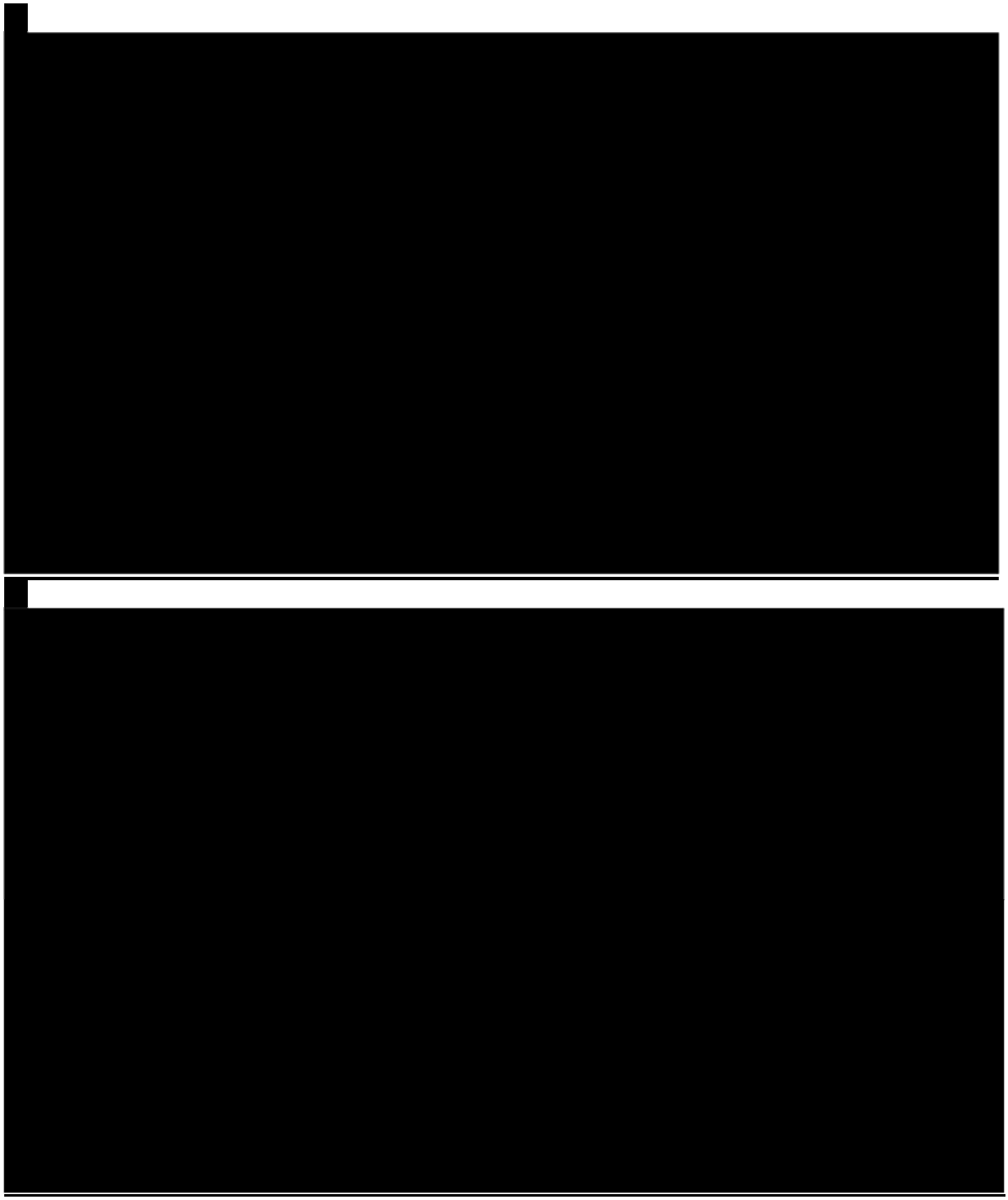
Table 9: Progression-free survival (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (n=53)	Overall (n=53)
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Earliest contributing event, n					
Disease Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	**STARTRK-1 (n=7)**	**STARTRK-2 (n=37)**	**Overall (n=53)**	**Overall (n=53)**
Patients without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)					
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; KM, Kaplan-Meier; NR, not reported.
Notes: Summaries of Time-to-Event (median, percentiles) are KM estimates; 95% CI for median was computed using the method of Brookmeyer and Crowley.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Figure 4: Progression-free survival (BICR Assessment) – Primary efficacy set



Key: BICR, blinded independent central review; CCOD, clinical cut-off date; CI, confidence interval; DBL, database lock; NSCLC, non-small cell lung cancer.
Notes: [a], primary integrated efficacy analysis, which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 31 May 2018 - DBL 31 July 2018; [b], updated integrated efficacy analysis which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 30 October 2018 - DBL 21 December 2018.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Results from the sensitivity analyses for PFS were consistent with the results from the primary approach, demonstrating robustness of the data. Further details of the sensitivity analyses, including results, are presented in Appendix L.3.

Entrectinib treatment also demonstrated a durable effect on systemic PFS in the secondary efficacy set. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), the median PFS in the secondary efficacy set as assessed by the BICR, was [redacted] months (95% CI: [redacted], [redacted]). However, the median PFS was not considered a stable estimate due to ongoing responses in a high proportion of patients: only [redacted] patients ([redacted]%) had an event (disease progression or death). Full details of the secondary efficacy set analyses are presented in Appendix L.4.

Time to central nervous system progression

Durability of treatment effect and potential protection against progression in the CNS was observed via time to first documentation of radiographic CNS disease progression or death due to any cause. As shown in Table 10, at the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), the median time to event was [redacted] ([redacted]; 95% CI: [redacted], [redacted]) in the primary efficacy set with a median follow-up for progression or death of 15.5 months.

Table 10: Time to CNS progression (BICR Assessment) – Primary efficacy set

	ALKA (n=9)	**STARTRK-1 (n=7)**	**STARTRK-2 (n=37)**	**Overall (n=53)**
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]
Earliest contributing event, n				
First New Lesion in CNS	[redacted]	[redacted]	[redacted]	[redacted]
Disease Progression	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	ALKA (n=9)	STARTRK-1 (n=7)	STARTRK-2 (n=37)	Overall (n=53)
Time to event (months)				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; KM, Kaplan-Meier; NE, not estimable.
Notes: Summaries of Time-to-Event (median, percentiles) are KM estimates; 95% CI for median was computed using the method of Brookmeyer and Crowley.
Source: Summary of clinical efficacy.[43]

Overall survival

Entrectinib treatment demonstrated a clear potential for long-term survival benefit in patients with ROS1-positive NSCLC (Table 11). At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), survival follow-up was 15.5 months (95% CI: 14.8, 19.0). The KM estimated median OS was [redacted] (95% CI: [redacted]) (Table 11) and only [redacted] patients ([redacted]%) had died at the time of analyses. At the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), OS data were still immature and median [redacted] – only [redacted] ([redacted]%) had died at the time of analyses. Figure 5a and Figure 5b present the KM curves for OS from the primary and the updated integrated efficacy analysis, respectively.

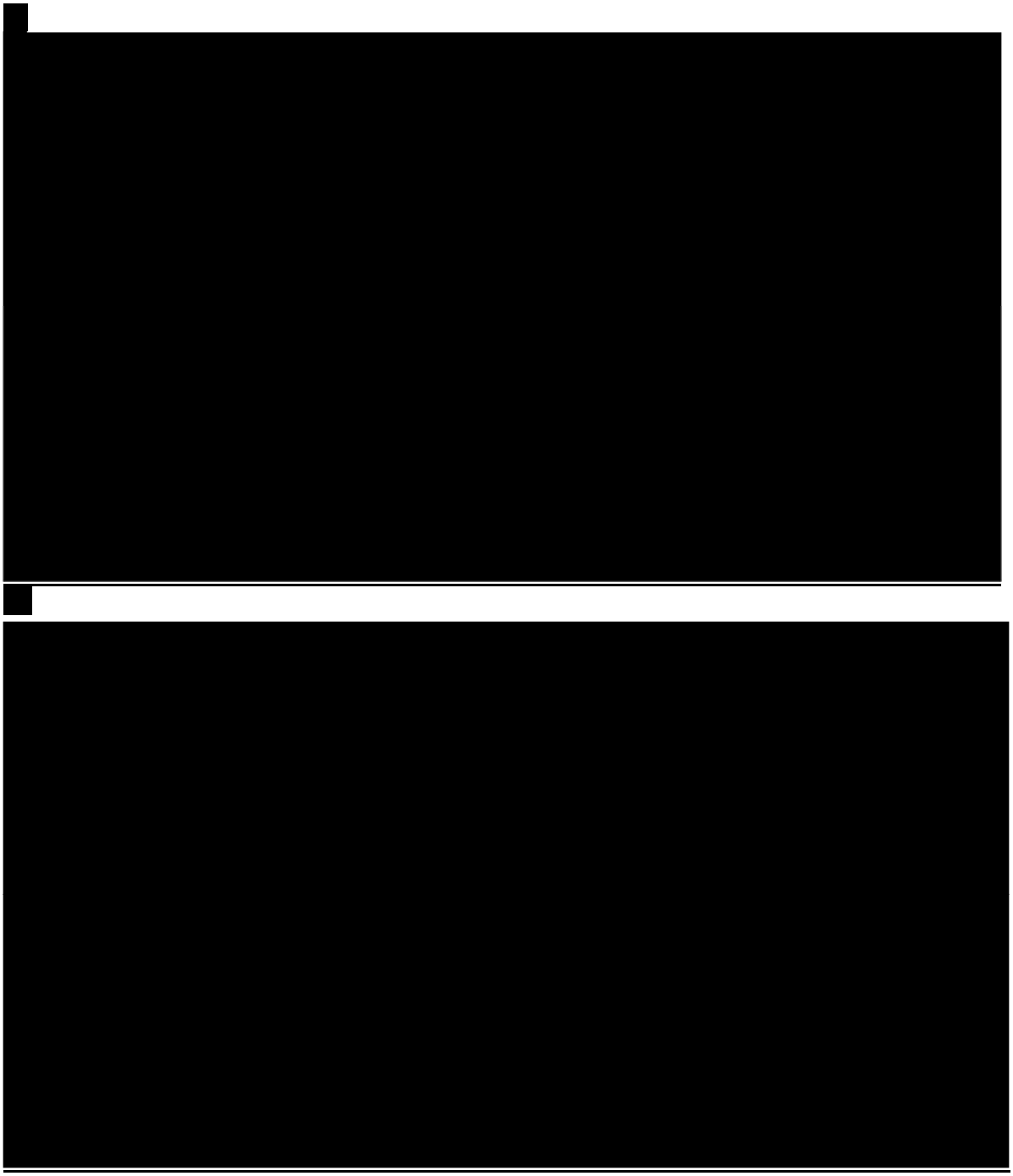
Table 11: Overall survival (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	**STARTRK-1 (n=7)**	**STARTRK-2 (n=37)**	**Overall (n=53)**	**Overall (n=53)**
Patients with event (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Earliest contributing event, n					
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)					
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	CCOD – 31 May 2018				CCOD – 30 Oct 2018
	ALKA (n=9)	**STARTRK-1 (n=7)**	**STARTRK-2 (n=37)**	**Overall (n=53)**	**Overall (n=53)**
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months					
Patients remaining at risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free probability (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable.
Notes: Summaries of Time-to-Event (median, percentiles) are KM estimates; 95% CI for median was computed using the method of Brookmeyer and Crowley.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Figure 5: Overall survival (BICR Assessment) – Primary efficacy set



Key: BICR, blinded independent central review; CCOD, clinical cut-off date; CI, confidence interval; DBL, database lock; NE, not estimable; NSCLC, non-small cell lung cancer.
Notes: [a], primary integrated efficacy analysis, which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 31 May 2018 - DBL 31 July 2018; [b], updated integrated efficacy analysis which includes ROS1-positive NSCLC patients in the primary efficacy set enrolled up to 30 April 2017 - CCOD 30 October 2018 - DBL 21 December 2018.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Patient reported outcomes

EORTC QLQ-C30 and QLQ-LC13

All patients in the ROS1-positive NSCLC efficacy evaluable analysis population in the START-TRK2 study (n=[redacted]) completed the QLQ-C30 and the QLQ-LC13. The number of patients with evaluable QLQ-C30 and QLQ-LC13 questionnaires at baseline were [redacted] and [redacted], respectively. The completion rates for QLQ-C30 and QLQ-LC13 were high at baseline ([redacted]% and [redacted]%, respectively) and the completion rate remained high (≥[redacted]%) at most study visits. By week 20, approximately [redacted]% of the original sample was still completing the QLQ-C30 and QLQ-LC13.

As shown in Table 12, at baseline, patients reported moderate-to-high functioning scores for QLQ-C30 (GHS [redacted], physical functioning [redacted], role functioning [redacted], and cognitive functioning [redacted]). While receiving entrectinib in STARTRK-2, patients tended to maintain or improve on high baseline HRQL, with mean changes at the end of treatment of [redacted] for the GHS.

For physical functioning, role functioning, and cognitive functioning, patients continued to report moderate-to-high scores at most study visits with a trend towards clinical improvement. Whereas, the cognitive functioning scale maintained its overall high baseline value and trended towards some worsening at specific timepoints that were above the clinical meaningful threshold of 10-points (worst mean change score of [redacted] at Cycle 22 Day 1).

According to the QLQ-LC13, patients reported moderate lung cancer specific symptom burden at baseline (chest pain [mean score=[redacted]], dyspnoea [mean score=[redacted]]; Table 13). Following treatment with entrectinib there were trends towards immediate clinical meaningful improvement. Severe cough was reported at baseline with a mean score of [redacted], followed by immediate marked clinical meaningful improvement on Cycle 2 Day 1 (mean change from baseline score of [redacted]). The lasagna plots (change from baseline) for chest pain, cough, and dyspnoea are presented in Appendix L.5.

Table 12: EORTC QLQ-C30 Scores from baseline to end of treatment

	Baseline	End of treatment	Change from baseline
Global health status			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]

	Baseline	End of treatment	Change from baseline
Median (range)	[redacted]	[redacted]	[redacted]
Physical Functioning			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Role functioning			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Cognitive functioning			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Symptom scale- Dyspnoea			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Symptom scale- Fatigue			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Key: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire;
Source: STARTRK-2 CSR.[42]

Table 13: EORTC QLQ-LC13 Scores from baseline to end of treatment

	Baseline	End of treatment	Change from baseline
Coughing			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Dyspnoea			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Pain in arm or shoulder			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Pain in chest			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Pain in other parts			
Mean (standard deviation)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Key: EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and Lung Cancer Module
Source: STARTRK-2 CSR.[42]

EQ-5D

All patients in the ROS1-positive NSCLC efficacy evaluable analysis population in the START-TRK2 study (n=[redacted]) completed the EQ-5D-3L questionnaire on Day 1 of each treatment cycle and at the end of treatment. The UK tariff was used to estimate utility measurements based on EQ-5D-3L outcomes for baseline and progression-based categories. These data are presented in Section B.3.4.

B.2.7. Subgroup analysis

In the pre-specified subgroup analyses in the primary integrated analysis, ORR was generally consistent in the subgroups with adequate numbers of patients, as summarised in Appendix E.

As described in Section B.2.4, the primary efficacy set was split into two important subpopulations: patients with CNS metastases at baseline and patients without CNS metastases at baseline. As shown in Table 14, entrectinib demonstrated clinically meaningful and durable systemic responses in patients irrespective of the presence of CNS metastases at baseline.

Of particular interest, entrectinib offers intracranial activity against ROS1-driven CNS metastases. As shown in Table 15, entrectinib treatment demonstrated intracranial responses of a similar magnitude to systemic responses in patients with CNS metastases at baseline. Entrectinib is the only ROS1 inhibitor to date to show intracranial activity against ROS1-driven CNS metastases, emphasising its efficacy.

Table 14: Summary of Efficacy by Baseline CNS Disease Status (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018		**CCOD – 30 Oct 2018**	
	Baseline CNS Disease Status[a]		**Baseline CNS Disease Status[a]**	
	No (n=[redacted])	**Yes (n=[redacted])**	**No (n=[redacted])**	**Yes (n=[redacted])**
Objective Response Rate[b]				
Responders, n	[redacted]	[redacted]	[redacted]	[redacted]
ORR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Best Overall Response, n (%)[c]				
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD[d]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/PD[de]	[redacted]	[redacted]	[redacted]	[redacted]
Missing or unevaluable[f]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of Response				
Patients with event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Benefit Rate				
CBR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

	CCOD – 31 May 2018		CCOD – 30 Oct 2018	
	Baseline CNS Disease Status[a]		Baseline CNS Disease Status[a]	
	No (n=[redacted])	Yes (n=[redacted])	No (n=[redacted])	Yes (n=[redacted])
Progression-Free Survival				
Patients with event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Overall Survival				
Patients with event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Key: BICR=blinded independent central review; CCOD, clinical cut-off date; CR, complete response; NR, not reported; ORR, objective response rate; PD, progressive disease.
Notes: [a], CNS disease status at baseline as determined by the investigator; [b], Objective response is defined as PR or CR confirmed by repeat-imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder; [c], Best Overall Response is derived per RECIST 1.1; [d], SD and Non-CR/Non-PD must be observed study day 35 or later, otherwise they count as NE; [e], Patients were categorised as having Non CR/PD if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator; [f], Missing or unevaluable category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response; CIs are calculated using the Clopper-Pearson method; g, median was extended due to censoring date changes in the later CCOD.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

Table 15: Overview of Intracranial Efficacy in Patients with Baseline CNS Disease Status (BICR Assessment) – Primary efficacy set

	CCOD – 31 May 2018		CCOD – 30 Oct 2018
	Patients with Measurable Disease (n=[redacted])	All Patients (n=[redacted])	All Patients (n=[redacted])
Intracranial Objective Response[a]			
Responders, n	[redacted]	[redacted]	[redacted]
ORR (95% CI)	[redacted]	[redacted]	[redacted]
Intracranial Best Overall Response, n (%)[b]			
CR	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
SD[c]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Non-CR/PD[cd]	[redacted]	[redacted]	[redacted]
Missing or unevaluable[e]	[redacted]	[redacted]	[redacted]
Duration of Intracranial Response			
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
Intracranial Progression-Free Survival			
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PD, progressive disease.
Notes: [a], Intracranial objective response is defined as PR or CR confirmed by repeat-imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder; [b], Intracranial best Overall Response is derived per RECIST 1.1; [c], SD and Non-CR/Non-PD must be observed study day 35 or later, otherwise they count as NE; [d], Patients were categorised as having Non CR/PD if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator; [e], Missing or unevaluable category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response; CIs are calculated using the Clopper-Pearson method.
Source: Summary of clinical efficacy;[43] D75 data summary.[45]

B.2.8. Meta-analysis

Integrated analyses form the primary evaluation of entrectinib in ROS1-positive NSCLC is presented in previous sections.

B.2.9. Indirect and mixed treatment comparisons

As detailed in Appendix D.1, a systematic literature review (SLR) was conducted to identify and select evidence on the efficacy and safety of entrectinib and comparator treatments for patients with locally advanced or metastatic ROS1-positive NSCLC who have either progressed following prior therapies or who have no acceptable standard therapies.

As described in Section B.1.3, it has been previously concluded that the ROS1-positive population is similar to the ALK-positive population as they are similar in terms of patient demographics (e.g. younger age, non-smoker or light smoking) and clinical characteristics (e.g. adenocarcinoma histologic type).[16, 22] As such, due to the paucity of evidence in the ROS1-positive NSCLC population, the SLR was extended to include ALK-positive NSCLC, and evidence for the ALK-positive NSCLC population has been used as a proxy for the pemetrexed chemotherapy comparisons.

Eleven prospective comparator trials were identified through the two SLRs that could be considered for inclusion in an ITC of interest to this appraisal. Eight of these studies were excluded during feasibility assessment (see Appendix D.1 for further details), meaning three trials provided the evidence base for comparator treatments utilised for the ITC.

The comparator evidence base included one trial for crizotinib in ROS1-positive NSCLC patients (PROFILE 1001), one trial for pemetrexed plus platinum with pemetrexed maintenance in treatment-naïve ALK-positive NSCLC patients (ASCEND-4), and one trial for chemotherapy (pemetrexed or docetaxel; PROFILE 1007) in treatment-exposed ALK-positive NSCLC patients. A comparative summary of the methods of these studies, and the integrated analysis for entrectinib is summarised in Table 16, and key patient characteristics are provided in Table 17. Full details of the results of the comparator studies used to populate the ITC are provided in Appendix D.1. Of note, there was a recent update to the PROFILE 1001 study presented at the European Lung Cancer Congress (ELCC) and subsequently released as pre-publication manuscript that provided updated survival data for ROS1-positive NSCLC patients treated with crizotinib.[47, 48] These data were

published after the formal SLR and ITC update but have been considered when interpreting the ITC outcomes, and reviewing survival extrapolation approaches in the modelling presented in Section B.3.3. It should also be noted that the primary integrated efficacy analyses with a CCOD of 31 May 2018 provided entrectinib data.

As can be seen from data presented in Table 16 and Table 17, there is observed heterogeneity across studies with regard to trial design and patient population. Key differences are listed below but the small patient numbers in the ROS1-positive NSCLC trials should be considered when interpreting proportions:

- Patients in the entrectinib integrated analysis and PROFILE 1001 had ROS1-positive NSCLC, whereas patients in ASCEND-4 and PROFILE 1007 had ALK-positive NSCLC.
- The proportion of patients with CNS metastases at baseline was not reported for PROFILE 1001. The study inclusion criteria stated that patients were required to have locally advanced or metastatic, histologically confirmed NSCLC positive for rearrangements in the ROS1 gene. The proportion of patients with locally advanced versus metastatic disease was also not reported.
- The proportion of patients with CNS metastases at baseline was slightly higher in the entrectinib integrated analysis at [redacted]% compared to approximately 30% in ASCEND-4 and PROFILE 1007 (though this could reflect the smaller patient numbers in the entrectinib trial population). CNS metastases are associated with a poorer prognosis.
- The entrectinib integrated analysis contained a lower proportion of patients who had never smoked than all other studies. PROFILE 1001 had no current smokers and the highest proportion of patients who had never smoked. ASCEND-4 had a higher prevalence (8.0%) of current smokers compared to other studies.
- The entrectinib integrated analysis had a higher proportion of patients with an ECOG performance status of 2 ([redacted]%, n=[redacted]) than any of the other studies. ECOG performance status of 2 may reflect more advanced disease.
- The proportion of patients with adenocarcinoma in the entrectinib integrated analysis was [redacted]%, which was lower than in the comparator studies. In each of the comparator studies the proportion with adenocarcinoma was >90% and the corresponding proportion with non-adenocarcinoma was <10% and the absolute

number of patients was <15. Therefore, the patient population in these trials essentially represents a population with adenocarcinoma.

- The entrectinib integrated analysis included a mixture of treatment naïve and treatment exposed patients. PROFILE 1001 also included a mixture of treatment naïve and treatment exposed patients (first-line n=7, second-line n=20, third-line n=13, fourth-line n=3 and fifth-line or greater n=10). Whereas, ASCEND-4 enrolled only treatment naïve patients and PROFILE 1007 enrolled only second-line patients. A rich treatment history may reflect more advanced disease and each treatment line is normally associated with worsening prognosis, but it could also be argued that only fitter patients can receive multiple treatment lines.
- As the entrectinib integrated analysis and the PROFILE 1001 study were single arm studies, treatment switching was not possible. Crossover was less common in ASCEND-4 (43.0%) compared to 64.0% in PROFILE 1007 but in both trials, patients progressing on chemotherapy could switch to ROS1-targeted treatment which could positively bias survival outcomes (in favour of chemotherapy).

Table 16: Comparative summary of studies considered for indirect treatment comparison

	Entrectinib integrated analysis	**PROFILE 1001**	**ASCEND-4**	**PROFILE 1007**
Study design	Pooled analysis of two phase I and one Phase II studies.	Phase I, single arm, safety and PK/PD study	Phase III, Randomised, Open-label Study	Phase III, Randomised, Open-label Study
Population	Adult patients with advanced ROS1-positive NSCLC	Adult patients with advanced ROS1-positive NSCLC	Adult patients with untreated, advanced, ALK-positive NSCLC	Adult patients with Crizotinib-naïve, Chemotherapy-experienced, ALK-positive NSCLC
Intervention	Entrectinib	Crizotinib	Ceritinib	Crizotinib
Comparator	N/A	N/A	Pemetrexed + cisplatin followed by pemetrexed maintenance	Pemetrexed or docetaxel
Primary endpoint	ORR assessed by BICR using RECIST v1.1.	ORR measured by RECIST assessed by	PFS BICR-assessed by RECIST v1.1	PFS assessed by independent radiologic review

	Entrectinib integrated analysis	PROFILE 1001	ASCEND-4	PROFILE 1007
		IRR and the investigator		
Median follow-up duration	16.6 months	NR	>33 months	≤112 weeks

Key: ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; N/A, not applicable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: Summary of clinical efficacy;[43] NICE TA529;[49] Soria *et al.* 2017;[50] Shaw *et al.* 2013.[51]

Table 17: Patient characteristics at baseline for studies considered for indirect treatment comparison

	Entrectinib integrated analysis (n=53)	PROFILE 1001 (n=53)	ASCEND 4 (n=187)	PROFILE 1007 (n=174)
Treatment	Entrectinib	Crizotinib	Pemetrexed + platinum followed by pemetrexed maintenance	Chemotherapy (Pemetrexed or docetaxel)
Age				
Years, median (range)	53.0 (46.0, 61.0)	55.0 (25.0, 81.0)	54.0 (22.0, 80.0)	49 (24.0, 85.0)
Sex, n (%)				
Male	19 (35.8)	23 (43.4)	73 (39.0)	78 (45.0)
Female	34 (64.2)	30 (56.6)	114 (61.0)	99 (55.0)
Race, n (%)				
Non-Asian	34 (64.2)	32 (60.4)	82 (44.0)	78 (45.0)
Asian	19 (35.8)	21 (39.6)	105 (56.0)	99 (55.0)
Smoking status, n (%)				
Never	31 (58.5)	40 (75.5)	122 (65.0)	111 (64.0)
Former	20 (37.7)	13 (24.5)	50 (27.0)	54 (31.0)
Current	2 (3.8)	NR	15 (8.0)	9 (5.0)
ECOG PS, n (%)				
0 or 1	47 (88.7)	52 (98.1)	175 (94.0)	160 (92.0)
2	6 (11.3)	1 (1.9)	11 (6.0)	14 (8.0)
Disease stage, n (%)				
IIIB	3 (5.7)	NR	5 (2.7)	16 (9.2)
IV (non-CNS)	4 (7.5)	NR	120 (64.1)	98 (56.3)
IV (CNS)	23 (43.4)	NR	62 (33.2)	60 (34.5)
Histology, n (%)				

	Entrectinib integrated analysis (n=53)	PROFILE 1001 (n=53)	ASCEND 4 (n=187)	PROFILE 1007 (n=174)
Adenocarcinoma	35 (76.1)	51 (96.2)	183 (93.0)	164 (94.0)
Non-adenocarcinoma	18 (23.9)	2 (3.8)	4 (7.0)	7 (4.0)
Molecular alterations, **n (%)**				
ROS1	53 (100.0)	53 (100.0)	0	0
ALK	0	0	187 (100.0)	174 (100.0)
Prior anticancer therapies, **n (%)**				
First line	17 (32.1)	7 (13.2)	9 (5.0)	NR
Second line	23 (43.4)	20 (37.7)	NR	NR
Third line	5 (9.4)	13 (24.5)	NR	NR
≥Third line	8 (15.1)	NR	NR	NR
Fourth line	NR	3 (5.7)	NR	NR
≥Fifth line	NR	10 (18.9)	NR	NR

Key: ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; NICE, National Institute for Health and Care Excellence; NR, not reported.
Source: Summary of clinical efficacy;[43] NICE TA529;[49] Soria *et al.* 2017;[50] Shaw *et al.* 2013.[51]

Endpoints reported by each of the four studies are summarised in Table 18. Results and details of the outcomes used to populate the ITC are provided in Appendix D.1.

Table 18: Summary of endpoints reported by each study included in the indirect treatment comparison

Endpoint	Entrectinib integrated analysis	PROFILE 1001	ASCEND-4	PROFILE 1007
Efficacy endpoints				
Overall survival	✓	✓	✓	✓
Progression-free survival	✓	✓	✓	✓
Overall response rate	✓	✓	✓	✓
Safety endpoints				
Any serious adverse event	✓	×	×	×
Any adverse event Grade 3+	>2%	>10%	>15%	>15%
Treatment discontinuation due to adverse event	✓	✓	✓	✓

Methods

To make an adjusted comparison between entrectinib patients and the comparative evidence source, individual entrectinib-treated patients were assigned statistical weights that adjust for their over- or under-representation relative to that observed in each comparative evidence source. After weighting, average baseline characteristics (mean and variance) were balanced between the selected entrectinib cohort(s) and the comparative evidence source. All analyses were performed in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[52]

Weights were derived using a matching adjusted indirect comparison (MAIC) – a form of propensity score weighting.[53, 54] A propensity score logistic regression model estimates the odds of being enrolled into the entrectinib cohort or the comparative evidence source.

After the matching procedure was conducted and the weights derived, efficacy outcomes were compared between balanced treatment groups using statistical tests that incorporate the derived weights. For OS and PFS, weighted KM curves were generated. Hazard ratio (HR) comparing entrectinib cohort(s) and the comparative evidence source were estimated using weighted Cox proportional hazards models. For ORR and treatment discontinuation due to adverse events (AEs), odds ratios (OR) comparing entrectinib cohort(s) and the comparative evidence source were estimated using the derived weights. For the comparative evidence source, rows of the pseudo-individual patient data (IPD) were given a weight of 1 for each analysis. Full details of the methodology for the MAICs are provided in Appendix D.1.

Results

As the primary comparisons of interest to the decision problem, results for entrectinib comparison to crizotinib and pemetrexed plus platinum in treatment-naïve patients are presented below. Results for entrectinib comparison to chemotherapy in treatment-exposed patients are provided in Appendix D.4.

PROFILE 1001- Crizotinib

For the comparison of entrectinib with PROFILE 1001 crizotinib, the final baseline characteristics selected for matching were sex, race (Asian vs. non-Asian), ECOG (0 vs. 1 or 2), smoking history, prior treatments (treatment naïve vs. prior treatment),

age and disease stage (Stage IIIB vs. Stage IV non-CNS metastasis vs. Stage IV CNS metastasis). See Appendix D.1 for full details of the estimation of MAIC weights for comparison of entrectinib versus PROFILE 1001 crizotinib.

Overall survival

For the outcome of OS, the HR for entrectinib versus crizotinib based on MAIC shows that treatment with entrectinib reduced the risk of death compared to crizotinib (HR: [redacted] 95% CI [redacted]; Table 19). The unadjusted entrectinib KM curve and the MAIC re-weighted KM curve for entrectinib are very similar (Figure 6). This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching. There were some data limitations, notably a low number of events (censoring was required for 70% of patients in PROFILE 1001 and [redacted]% of patients in the entrectinib integrated analyses), meaning median time to event is not reached for any intervention. This and the small sample size leads to increased uncertainty in the results as indicated by relatively wide CIs around the HR.

The updated data presented at ELCC 2019 and reported a median OS for crizotinib of 51.4 months (95% CI: 29.3, not reached) based on a 49.1% event rate (26 deaths observed at the time of analysis).[48] The more mature KM curve (provided in Appendix D.1) does not have the long tail from 15 months onwards that is observed in the curve used for this ITC. This means the area under the curve will be smaller and the relative benefit for entrectinib would likely be larger should these data be used to update the MAIC.

Table 19: Comparison of entrectinib versus PROFILE 1001 crizotinib – Overall Survival

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	16	NR (NR, NR)	

Key: CI, confidence interval, NR, not reached; MAIC, matching adjusted indirect comparison.
Source: Summary of clinical efficacy;[43] NICE TA529.[49]

Figure 6: Kaplan–Meier Plot of Overall Survival – entrectinib versus PROFILE 1001 crizotinib

Progression-Free Survival

It was unclear if PFS reported in PROFILE 1001 was IA or by BICR. Therefore, we performed separate comparisons of PFS BICR and PFS IA data from the entrectinib integrated analyses with PFS data reported in PROFILE 1001.

PFS BICR

MAIC of PFS BICR data from the entrectinib integrated analyses relative to PFS data from crizotinib treated patients in PROFILE 1001 resulted in a HR close to 1 indicating that the risk of progression was similar for both treatments (HR: 95% CI (Table 20). There is an apparent difference in median PFS for both treatments: months for entrectinib compared to 19.15 months for crizotinib. However, the KM curve shows that there is effectively little difference in the probability of PFS between treatments from months to 26 months. The

unadjusted entrectinib KM curve and the MAIC re-weighted KM curve for entrectinib are very similar (Figure 7). This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching.

Table 20: Comparison of entrectinib versus PROFILE 1001 crizotinib – Progression-Free Survival by BICR

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	26	19.151 (14.708, NR)	

Key: CI, confidence interval, NR, not reached; MAIC, matching adjusted indirect comparison.
Source: Summary of clinical efficacy;[43] NICE TA529;[49]

Figure 7: Kaplan–Meier Plot of Progression-Free Survival by BICR – entrectinib versus PROFILE 1001 crizotinib

PFS IA

The HR for entrectinib versus crizotinib based on MAIC suggests that treatment with entrectinib is associated with a higher risk of disease progression relative to crizotinib (HR: [redacted] 95% CI [redacted]; Table 21). This is reflected in the shorter median PFS for patients treated with entrectinib compared to those receiving crizotinib. The unadjusted entrectinib KM curve and the MAIC re-weighted KM curve for entrectinib are again very similar (Figure 8). This supports the conclusion that the two study populations were already quite similar prior to matching.

Table 21: Comparison of entrectinib versus PROFILE 1001 crizotinib – Progression-Free Survival by IA

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	26	19.151 (14.708, NR)	

Key: CI, confidence interval, NR, not reached; MAIC, matching adjusted indirect comparison.
Source: Summary of clinical efficacy;[43] NICE TA529.[49]

Figure 8: Kaplan–Meier Plot of progression-free survival by IA – entrectinib versus PROFILE 1001 crizotinib

ORR

For the outcome of ORR, the OR for entrectinib versus crizotinib presented in Table 22 suggests that the adjusted entrectinib population is associated with significantly higher ORR compared to crizotinib. This indicates that entrectinib is significantly more effective than crizotinib. This is supported by a larger percentage of patients with ORR ([redacted] for entrectinib compared to 62.3% for crizotinib). The unadjusted entrectinib ORR and the MAIC re-weighted entrectinib ORR are quite similar. This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching.

Table 22: Comparison of entrectinib versus PROFILE 1001 crizotinib – ORR

Intervention	Comparator	Sample Size	Number with ORR	% with ORR	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	33	62.26	

Key: CI, confidence interval; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; ORR, objective response rate.
Source: Summary of clinical efficacy.[43] NICE TA529.[49]

Discontinuation due to AEs

For the outcome of treatment discontinuation due to adverse events, the OR for entrectinib versus crizotinib presented in Table 23 suggests that the adjusted entrectinib population is associated with lower odds of discontinuation due to AEs compared to crizotinib. This indicates that entrectinib leads to less discontinuations due to adverse events than crizotinib. The CI around the estimated OR is quite wide. This suggests that the estimate is quite uncertain. This is supported by the lower percentage of patients with discontinuation due to AE ([redacted] for entrectinib compared to 7.5% for crizotinib. The conclusion here is that there is no significant difference between the treatments. The unadjusted entrectinib percentage with discontinuation due to AEs is higher ([redacted]%) than the MAIC re-weighted entrectinib percentage with discontinuation due to AEs. This suggests that those patients with discontinuation due to AEs tended to be given a lower weight.

Analysis for this outcome is based on the ROS1-positive safety population (n=[redacted]) from the entrectinib integrated analyses. The MAIC method matching on the characteristics of the safety population led to a patient population that is the same as the PROFILE 1001 population (Appendix D.1).

Table 23: Comparison of entrectinib versus PROFILE 1001 crizotinib – Discontinuation due to AEs

Intervention	Comparator	Sample Size	Number of discontinuations due to AEs	% discontinuation due to AEs	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	4	7.54	

Key: AE, adverse event; CI, confidence interval; MAIC, matching-adjusted indirect comparison.
Note: This is based on the patients in the safety set (n=134)
Source: Summary of clinical efficacy;[43] NICE TA529;[49]

ASCEND-4 – pemetrexed plus platinum with pemetrexed maintenance

For the comparison of entrectinib with ASCEND-4, the final baseline characteristics selected for matching were sex, race (Asian vs. non-Asian), ECOG (0 vs. 1 or 2), smoking history, age and disease stage (Stage IIIB vs. Stage IV non-CNS metastasis vs. Stage IV CNS metastasis). See Appendix D.1 for full details of the estimation of MAIC weights for comparison of entrectinib versus ASCEND-4.

Overall Survival

For the outcome of OS, the HR for entrectinib versus pemetrexed plus platinum with pemetrexed maintenance based on MAIC shows that treatment with entrectinib significantly reduced the risk of death compared to pemetrexed plus platinum followed by pemetrexed maintenance (HR: [redacted], 95% CI [redacted]; Table 24). The unadjusted entrectinib KM curve and the MAIC re-weighted KM curve for entrectinib are very similar (Figure 9). This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching. There were some data limitations, notably a low number of events in the entrectinib integrated analyses (as noted previously censoring was required for 83%

of patients), meaning median time to event is not reached for entrectinib. The upper limit of the 95% CI for median time to event in the pemetrexed plus platinum with pemetrexed maintenance arm was not reached. This indicates that the data are not mature for this trial either, and therefore the magnitude of the relative benefit is still uncertain.

Table 24: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – Overall survival

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Pemetrexed + Platinum with Pemetrexed Maintenance		187	86	26.264 (22.840, NR)	

Key: CI, confidence interval, MAIC, matching-adjusted indirect comparison; NR, not reached.
Source: Summary of clinical efficacy;[43] Soria *et al.* 2017.[50]

Figure 9: Kaplan–Meier Plot of Overall Survival – entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance

Progression-free survival (BICR)

For the outcome of PFS, the HR for entrectinib versus pemetrexed plus platinum with pemetrexed maintenance based on MAIC shows that treatment with entrectinib significantly reduced the risk of progression compared to pemetrexed plus platinum with pemetrexed maintenance (HR: [redacted], 95% CI [redacted]; Table 25). This was supported by longer median PFS for patients treated with entrectinib ([redacted] months) compared with 8 months for patients treated with pemetrexed plus platinum with pemetrexed maintenance. The unadjusted entrectinib KM curve and the MAIC re-weighted KM curve for entrectinib are very similar (Figure 10). This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching.

Table 25: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – Progression-free survival by BICR

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Pemetrexed + Platinum with Pemetrexed Maintenance		53		7.986 (5.700, 11.135)	

Key: CI, confidence interval, MAIC, matching-adjusted indirect comparison; NR, not reached.
Source: Summary of clinical efficacy;[43] Soria *et al.* 2017.[50]

Figure 10: Kaplan–Meier Plot of Progression-Free Survival by BICR – entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance

ORR

For the outcome of ORR, the OR for entrectinib versus pemetrexed plus platinum with pemetrexed maintenance presented in Table 26 suggests that the adjusted entrectinib population is associated with significantly higher ORR compared to pemetrexed plus platinum with pemetrexed maintenance. This is supported by a larger percent of patients with ORR, [redacted] for entrectinib compared to 26.7% for pemetrexed plus platinum with pemetrexed maintenance. The unadjusted entrectinib ORR and the MAIC re-weighted entrectinib ORR are quite similar. This shows that re-weighting has only a small effect which indicates that the two study populations were already quite similar prior to matching.

Table 26: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – ORR

Intervention	Comparator	Sample Size	Number with ORR	% with ORR	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Pemetrexed + Platinum with Pemetrexed Maintenance		187	50	26.74	

Key: CI, confidence interval, MAIC, matching-adjusted indirect comparison; ORR, objective response rate.
Source: Summary of clinical efficacy[43]; Soria *et al.* 2017.[50]

Discontinuation due to AEs

For the outcome of treatment discontinuation due to adverse events, the OR for entrectinib versus pemetrexed plus platinum with pemetrexed maintenance is close to 1 which suggests treatment discontinuation due to adverse events is similar for both treatments (OR: [redacted], 95% CI [redacted]; Table 27). This is supported by the similar percentage of patients with discontinuation due to AEs, [redacted] for entrectinib compared to 8.6% for pemetrexed plus platinum with pemetrexed maintenance. The unadjusted entrectinib percentage with discontinuation due to AEs is higher ([redacted]%) than the MAIC re-weighted entrectinib percentage with discontinuation due to AEs. This suggests that those patients with discontinuation due to AEs tended to be given a lower weight.

Analysis for this outcome is based on the ROS1-positive safety population (n=[redacted]) from the entrectinib integrated analyses. The MAIC method matching on the characteristics of the safety population led to a patient population that is the same as the ASCEND-4 population (Appendix D.1).

Table 27: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – Discontinuation due to AE

Intervention	Comparator	Sample Size	Number of discontinuations due to AE	% discontinuation due to AE	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Pemetrexed + Platinum with Pemetrexed Maintenance		187	16	8.56	

Key: AE, adverse event; CI, confidence interval; MAIC, matching-adjusted indirect comparison.
Note: This is based on the patients in the safety set (n=134)
Source: Summary of clinical efficacy;[43] Soria *et al.* 2017.[50]

Conclusions

In the comparison of entrectinib with PROFILE 1001 crizotinib, entrectinib improved OS and significantly increased the ORR relative to crizotinib. Treatment discontinuations due to adverse events were similar for entrectinib and crizotinib. It was unclear if PFS reported in PROFILE 1001 was IA or assessed by BICR. Therefore, we performed separate comparisons of PFS IA and PFS BICR data from pooled entrectinib studies with PFS data reported in PROFILE 1001. For the comparison using PFS assessed by BICR for entrectinib, the HR showed no difference between treatments. In contrast, for the comparison using PFS IA for entrectinib, there was an increase in the risk of progression for entrectinib compared to crizotinib.

In the comparison with ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance, entrectinib significantly improved OS, PFS and ORR. Entrectinib also led to a similar number of discontinuations due to AEs compared to pemetrexed plus platinum with pemetrexed maintenance.

Uncertainties in the indirect treatment comparison

There was marked heterogeneity across the entrectinib integrated analyses and comparator studies with regard to trial design and patient population. There are very

limited data for the ROS1-positive NSCLC patients, which meant results in ALK-positive NSCLC patients had to be used as a proxy in the comparative efficacy analyses for the pemetrexed plus platinum with pemetrexed maintenance comparison. While this approach is not ideal and ROS1 fusions define a unique molecular subset of oncogenic drivers, ALK-positive and ROS1-positive NSCLC are similar in terms of patient demographics (e.g. younger age, non-smoker or light smoking) and clinical characteristics (e.g. adenocarcinoma histologic type),[16, 22] and clinical consultation endorsed the approach taken in consideration of the data limitations.[3] Furthermore, a proxy assumption was used in the recent NICE appraisal for crizotinib for treating ROS1-positive advanced NSCLC.[38] Although the committee acknowledged that using data from a proxy population is far from ideal, after taking into account the relatively small patient population and the clinical experts' views, they agreed to explore the proxy data in its decision-making.[38] Crizotinib is now recommended for use within the CDF as an option for treating ROS1-positive advanced NSCLC in adults.

There was high uncertainty in the MAIC results as demonstrated by the width of the 95% CI. This is driven not only by the small sample sizes in the ROS1-positive NSCLC patient groups, but also by the low number of events in some outcomes, most notably OS where censoring was required for a high proportion of patients in some trials, which further restricts the interpretation of results. Indeed, for the entrectinib integrated analyses, censoring was required for [redacted]% of patients in the OS estimates, warranting caution to be applied when interpreting survival analyses from the MAIC. The small sample sizes further limit the number of variables which can be used in matching. Nonetheless, consistent trends in favour of entrectinib were observed for most outcomes across comparisons made that are predominantly suggestive of a clinical benefit to be achieved with this treatment. In the case of the comparison to pemetrexed plus platinum with pemetrexed maintenance for OS, estimated relative effect can be considered conservative given several patients in the chemotherapy arm of ASCEND-4 received ROS1-targeted treatment on progression.

The only exception to trends in favour of entrectinib was in analyses of entrectinib versus crizotinib for PFS when using IA data for entrectinib. These data may not be comparable (PFS assessment methods were not fully detailed for the PROFILE

1001 study provided crizotinib data) and are not supported by the OS comparison that falls in favour of entrectinib. Real world progression data for crizotinib from a UK clinical audit by the Royal Marsden reported a median PFS of 12.1 months,[38] and data from retrospective studies identified through SLR reported a median PFS range of 5.5 to 15 months with crizotinib.[20, 35, 55-57] These are markedly shorter estimates than the median PFS of 19.2 months reported in the PROFILE 1001 study and used in the ITC presented. It was noted by the ERG involved in the crizotinib technology appraisal that the PROFILE 1001 analysis lacked face validity with modelled survival based on these data resulting in very long projections,[58] and real-world experience of crizotinib effectiveness is reported to be of a lower magnitude than observed in the PROFILE 1001 trial.[3]

Flatiron data of ROS1-positive NSCLC patients receiving crizotinib treatment in US real world practice similarly report a shorter progression free period with a median PFS of 8.8 months observed in 69 patients meeting the eligibility criteria of STARTRK-2. When these data are used to indirectly compare entrectinib versus crizotinib, a significantly lower risk of disease progression is observed (PFS HR: 0.44 [95% CI: 0.26, 0.75]). Full details of this analysis and further ITC analyses using Flatiron data are provided in Appendix D.5.

Finally, it should be noted that the ITC was conducted prior to the release of the updated integrated efficacy analyses for entrectinib, and prior to the publication of more mature OS data for crizotinib from PROFILE 1001. The updated integrated efficacy analyses for entrectinib is fully supportive of the primary integrated efficacy analyses and therefore outcomes of the ITC would be expected to align to those based on the earlier data cut. With regard to the more mature OS data for crizotinib, these are only likely to further support the estimated extension of survival with entrectinib.

In summary, the approach taken to ITC recognises the uncertainties and limitations and attempts to provide the most robust analyses possible to aid decision making in their presence. However, in further recognition of data paucity at this time, entrectinib is considered to be a direct candidate for reimbursement through the CDF.

B.2.10. Adverse reactions

No additional studies to the integrated analyses reported AEs for entrectinib in the ROS1-positive NCLSC patient population. Safety analyses presented below are for the ROS1 safety population from ALKA, STARTRK-1 and STARTRK-2 (n=[redacted]), and the total safety population from ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG (n=[redacted]), as described in Section B.2.4.

Treatment exposure

All patients from Study STARTRK-NG and some patients from ALKA and STARTRK-1 were administered entrectinib based on body surface area (BSA; mg/m^2) during the dose escalation phase. For the analyses described in this section, all dose amounts were reported in mg as reported in the study electronic Case Report Form.

At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), [redacted] ROS1-positive NSCLC patients and [redacted] patients overall had received at least one dose of entrectinib (Table 28). Most ROS1-positive patients received all of their planned doses of entrectinib, with few missed doses; the median number of missed doses was [redacted] (range: [redacted]) and the median duration of exposure to entrectinib was [redacted] months (range: [redacted] months), corresponding to a median of [redacted] cycles (range: [redacted]). Similar results were observed in the total safety population treated with entrectinib (Table 28). In the primary efficacy set, the median treatment duration with entrectinib was longer at [redacted] months, corresponding to a median of [redacted] cycles.

Table 28: Summary of extent of exposure to entrectinib in the ROS1 safety population and all patients treated with entrectinib

	ROS1 safety population (n=[redacted])	**Total safety population (n=[redacted])**
Median treatment duration, months (range)[a]	[redacted]	[redacted]
Median no. of cycles (range)	[redacted]	[redacted]
Median no. of missed doses (range)	[redacted]	[redacted]
Mean cumulative dose, mg (SD)	[redacted]	[redacted]
Median dose intensity, % (range)[b]	[redacted]	[redacted]

Key: SD, Standard Deviation.
Notes: [a], Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day; [b], defined as total cumulative dose actually received/total planned dose x 100%. Factors

contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.
Source: Summary of clinical safety[59]

Adverse events

An overview of the AEs for the ROS1 safety population and the total safety population is presented in Table 29. [redacted] ROS1-positive patients ([redacted]%) experienced at least one AE (all grade), and [redacted]% were considered related to treatment. Grade 3 or higher AEs were experienced by [redacted]% of ROS1-positive patients and [redacted]% of these were considered treatment related. Most AEs requiring intervention were managed with dose interruption ([redacted]% of patients) or dose reduction ([redacted]% of patients). AEs leading to discontinuation of entrectinib were reported in [redacted]% of ROS1-positive patients. Similar results were observed in the total population treated with entrectinib (Table 29).

Table 29: Overview of Adverse Events in the ROS1 safety population and in all patients treated with entrectinib

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Any AE	[redacted]	[redacted]
Treatment related AEs	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]
Serious treatment related AEs	[redacted]	[redacted]
Grade ≥3 AEs	[redacted]	[redacted]
Grade ≥3 treatment related AEs	[redacted]	[redacted]
AEs Leading to Discontinuation	[redacted]	[redacted]
Treatment related AEs Leading to Discontinuation	[redacted]	[redacted]
AEs Leading to Dose Reduction	[redacted]	[redacted]
Treatment related AEs Leading to Dose Reduction	[redacted]	[redacted]
AEs Leading to Drug Interruption	[redacted]	[redacted]
Treatment related AEs Leading to Drug Interruption	[redacted]	[redacted]
AEs Leading to Death	[redacted]	[redacted]

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0; includes AEs with start date on or after the date of first dose of study treatment and up to and including 30 days after the last dose of study treatment, or events with start date prior to the date of first dose of study treatment, and worsened in severity or become serious during treatment.
Source: Summary of clinical safety[59]

Common adverse events

The AEs that occurred in ≥10% of patients in the ROS1 safety population and in the total safety population are summarised in Table 30. The most frequently reported AEs in ROS1-positive patients were constipation ([redacted]%), dysgeusia ([redacted]%), dizziness ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), dyspnoea ([redacted]%), oedema peripheral ([redacted]%), fatigue ([redacted]%), nausea ([redacted]%) and cough ([redacted]%). Similar results were observed in the total population treated with entrectinib (Table 30).

Table 30: Common Adverse Events reported in ≥10% of patients in the ROS1 safety population or in all patients treated with entrectinib

AE, n (%)	**ROS1 safety population (n=[redacted])**	**Total safety population (n=[redacted])**
Any AE	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Pain in extremities	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Blood creatine increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0. Percentages are based on N in the column heading. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately. Adverse Events appear in this table if the incidence in any Study Basket is >= 5%.
Source: Summary of clinical safety[59]

Treatment related adverse events

Treatment related AEs that occurred in ≥10% of patients in the ROS1 safety population and in the total safety population are presented in Table 31. The most frequently reported treatment related AEs in ROS1-positive patients were dysgeusia ([redacted]%), dizziness ([redacted]%), constipation ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), and fatigue ([redacted]%). Similar results were observed in the total population treated with entrectinib (Table 31).

Table 31: Treatment related AEs reported by ≥10% of patients in the ROS1 safety population or in all patients treated with entrectinib

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Any treatment related AE	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Blood creatine increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Source: Summary of clinical safety[59]

Grade ≥3 adverse events

Table 32 presents the Grade 3 or higher AEs reported in ≥2% of patients in the ROS1 safety population and in the total safety population. Grade 3 or higher AEs were reported in [redacted]% of ROS1-positive patients, the most frequently reported Grade 3 or higher AEs were weight increased ([redacted]%), dyspnoea ([redacted]%), urinary tract infection ([redacted]%), alanine aminotransferase increased ([redacted]%), pulmonary embolism ([redacted]%), neutropenia ([redacted]%) and pneumonia ([redacted]%). Generally similar results were observed in the total population treated with entrectinib (Table 32).

Table 32: Grade 3 or higher adverse events reported in ≥2% of patients in the ROS1 safety population or in all patients treated with entrectinib

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Any grade ≥3 AEs	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Rash	[redacted]	[redacted]

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0; Percentages are based on N in the column heading; For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once; For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Source: Summary of clinical safety[59]

Deaths

A summary of all deaths in the in the ROS1-positive safety population and in all patients treated with entrectinib is presented in Appendix L.6.

There was a total of [redacted] ([redacted]%) deaths in the ROS1 safety population and [redacted] ([redacted]%) in the total safety population. The rate of deaths that occurred within 30 days of the last dose of entrectinib ([redacted]%) was higher than the rate of deaths that occurred more than 30 days after the last dose of entrectinib ([redacted]%) for the ROS1 safety population; similar rates were observed at both timepoints for the total population treated with entrectinib ([redacted]% versus [redacted]%, respectively). The most common reason for death was progression of the underlying disease, which accounted for at least [redacted]% of all deaths.

A summary of fatal AEs in the ROS1 safety population and in all patients treated with entrectinib is also provided in Appendix L.6.

Grade 5 AEs occurred in [redacted]% of patients in the ROS1 safety population and in [redacted]% of patients in the total safety population; [redacted] Grade 5 AEs were assessed by the investigator as related to entrectinib.

Other serious adverse events

Serious AEs (SAEs)that occurred in ≥2% of patients in the ROS1 safety population and in the total safety population are presented in Table 33. Overall, [redacted]% of ROS1-positive patients experienced at least one SAE and [redacted]% were considered related to treatment (Table 29),the most frequently reported SAEs were pneumonia ([redacted]%), dyspnoea ([redacted]%) and pyrexia ([redacted]%). Similar results were observed in the total population treated with entrectinib (Table 33).

Table 33: Serious adverse events reported in ≥2% of patients in the ROS1 safety population or in all patients treated with entrectinib

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Any serious AEs	[redacted]	[redacted]
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0.
Percentages are based on N in the column heading. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately
Source: Summary of clinical safety[59]

Adverse events that led to withdrawal of study drug, dose interruption or dose reduction

A summary of AEs leading to withdrawal, dose interruption or dose reduction is provided in L.6.

AEs leading to withdrawal occurred in [redacted]% of ROS1-positive patients and were reported across a variety of system organ classes, with the most frequently reported being respiratory thoracic and mediastinal disorders ([redacted]%), gastrointestinal disorders ([redacted]%), cardiac disorders ([redacted]%), and nervous system disorders ([redacted]%). There was no a predominant AE that led to withdrawal of entrectinib. Similar results were observed in the total safety population.

AEs leading to dose interruption were reported in [redacted]% of ROS1-positive patients. The most frequently reported AEs leading to dose interruption were dizziness ([redacted]%), cognitive disorder ([redacted]%), blood creatine increased ([redacted]%), dyspnoea ([redacted]%), and pleural effusion ([redacted]%). Similar results were observed in the total safety population.

AEs leading to dose reduction were reported in [redacted]% of ROS1-positive patients. The most frequently reported AEs leading to dose interruption were dizziness ([redacted]%) and blood creatine increased ([redacted]%). Similar results were observed in the total safety population.

Safety profile summary

Entrectinib is a tolerable therapy with a manageable and reversible safety profile, and a clear risk management plan is available to provide support for clinicians and patients in the safe use of entrectinib.[60]

In the ROS1 safety population of the integrated analyses, entrectinib treatment discontinuations rate due to AEs was low ([redacted]%), with AEs generally managed through dose modifications or supportive care. Importantly, [redacted] deaths related to entrectinib treatment were observed. Overall, the type and severity of the AEs reported in the ROS1 safety population were generally consistent with their underlying disease or have been previously observed with entrectinib use in clinical trials. The safety outcomes observed in the ROS1 safety population were consistent with those observed in all patients treated with entrectinib. As such, the ROS1 safety population data are used in the model to align with the decision problem (Section B.3.4).

As demonstrated in an ITC (See Section B.2.9) entrectinib led to a similar number of discontinuations due to AEs compared to comparator treatments of crizotinib and pemetrexed plus platinum with platinum maintenance, but some differences in the safety profiles of these treatments have been noted. A naïve comparison of AEs across entrectinib and crizotinib suggest higher rates (>10% difference for any grade or >5% difference for Grade ≥3 events) of vision disorders, gastrointestinal disorders (vomiting and nausea), bradycardia, decreased appetite, neuropathy, oedema, rash, upper respiratory infection and Grade 3/4 neutropenia with crizotinib and higher rates of dysgeusia, myalgia and weight increase (any grade and Grade ≥3).[58, 59] Limitations of this naïve comparison should be acknowledged, including the small patient numbers in the ROS1 safety population of PROFILE 1001 that need considering when interpreting proportions. However, differences in the level of special warnings for use across SmPCs of crizotinib and entrectinib further suggest a

favourable safety profile for entrectinib. Details of the naïve comparison of AEs and SmPC special warnings are summarised in Appendix F.

The potential toxicity of chemotherapy is well known with myelosuppression, gastrointestinal toxicity and the associated severe dehydration of specific concern to the safety of patients.[61] In the PROFILE 1014 trial that compared crizotinib to pemetrexed plus platinum in ALK-positive NSCLC patients, increased myelosuppression was observed in the chemotherapy group with higher rates of neutropenia, leukopenia and thrombocytopenia but gastrointestinal disorders (vomiting and diarrhoea) were reported more frequently in the crizotinib arm.[62]

B.2.11. Ongoing studies

The three entrectinib studies ALKA, STARTRK-1 and STARTRK-2 used in the ROS1-positive NSCLC integrated analysis are currently ongoing. Furthermore, clinical data collection in addition to the ongoing studies will be explored as part of the CDF application. A prolonged follow-up of patients, potentially up to 5 years, will provide data to not only resolve uncertainties around mature outcomes of entrectinib in ROS-1 positive NSCLC patients, but also contribute to the limited literature defining these patients (see Section B.2.9).

Should NICE deem entrectinib to be eligible for CDF inclusion, proposed studies that will utilise CDF data are listed below:

- Systemic Anti-Cancer Therapy (SACT) dataset and Blueteq database
  - During the managed access arrangement, the primary source of data collection will be data collated by Public Health England (PHE), SACT is developed from routinely-captured data during the agreed access period
  - NHS England's Blueteq database primarily captures the CDF population; this data is shared with PHE for CDF evaluation purposes
  - Data collected from SACT will support data collected within the three clinical trials, namely: age, performance status, sex, outcome summary, reasons for treatment discontinuation, treatment duration, OS, treatment history
- European Thoracic Oncology Platform (ETOP) Registry data

  - ETOP is an anonymised data registry on patient cases and their tumour samples, that can be utilised for data extraction. The platform supports and collates data from research projects and clinical trials within thoracic malignancies
  - The data collected from here will be to (i) explore clinicopathological characteristics, treatment options, presence of other molecular alterations and clinical outcomes in this patient population (ii) understand biomarker testing landscape and tests currently being used for NTRK and ROS1 assessment, primarily across Europe, with an analysed UK subpopulation and (iii) collect longer-term survival outcomes
- Flatiron, United-States based Oncology database
  - Given the rarity of the condition, a proposal to utilise oncology data from the United-States is of interest in order to further understand the natural history and epidemiology of ROS-1 positive NSCLC patients
  - Data collected would pertain to demographics, clinical characteristics, treatment sequencing, outcomes of ROS-1 positive NSCLC patients with standard of care, and outcomes of those with and without CNS metastases at baseline

[redacted]

B.2.12. Innovation

The ROS1-positive integrated analysis for entrectinib provides further evidence that use of ROS1 inhibitors should be considered standard of care for adult patients with ROS1-positive advanced NSCLC.

Entrectinib for ROS1-positive NSCLC was granted Priority Review by the FDA.[63] The FDA grants Priority Review to medicines determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease and priority review is designed to take action on an application within six months of it being submitted.[64]

Entrectinib is the first ROS1 Inhibitor to show intracranial activity against ROS1-driven CNS metastases, which has led to entrectinib receiving Promising Innovative Medicine (PIM) designation for the patient group (PIM 2018/0021). However, due to small patient numbers, this group could not be separately modelled. Therefore, the impact of entrectinib on health-related benefits in this difficult-to-treat patient population with significant unmet need in current practice, is not fully captured in the quality-adjusted life year (QALY) calculation presented in Section 0.

Although no significant improvements in HRQL were observed following treatment with entrectinib, there were trends towards improvements in HRQL of ROS1-positive advance NSCLC patients. To date, entrectinib is the only ROS1 inhibitor that has demonstrated trends towards improvement in HRQL using a disease-specific instrument directly within a clinical trial. Prolonging systemic PFS as well as improving intracranial response rates and prolonging IC-PFS in real-would clinical practice, would be expected to have significant impacts on the daily activity and lives of patients and carers.

B.2.13. Interpretation of clinical effectiveness and safety evidence

As described in Section B.1, ROS1-positive NSCLC represents a rare (1–2% of cases), serious and life-threatening distinct molecular subset of NSCLC, with only one currently licensed targeted therapy in the UK. Entrectinib offers a further targeted treatment option with improved clinical effectiveness and tolerability compared to non-targeted chemotherapy, and proven CNS efficacy and thus meets an unmet medical need in current clinical practice.

Principal findings from the available clinical evidence to support entrectinib

Entrectinib treatment resulted in a clinically meaningful and durable systemic response. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), ORR was [redacted]%, median DoR among responders was [redacted] months

and median PFS was [redacted] months in the primary efficacy (n=53) set. Entrectinib also demonstrated potentially durable protection against progression in the CNS in the primary efficacy set, as median time to event was [redacted]. Data at the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), was similar to those observed in the primary integrated efficacy analysis.

Entrectinib demonstrated clinically meaningful and durable systemic responses in patients irrespective of the presence of CNS metastases at baseline. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), in patients with and without CNS metastases at baseline, ORR was [redacted]% and [redacted]% and DoR among responders was [redacted] months and [redacted], respectively. Systemic PFS observed in patients with and without CNS metastases at baseline was meaningfully durable ([redacted] months and [redacted] months, respectively), indicating activity against CNS metastatic disease and a possible protective effect against CNS progression. Data at the time of the updated integrated efficacy analysis (CCOD of 30 October 2018), was similar to those observed in the primary integrated efficacy analysis.

Entrectinib is the first ROS1 Inhibitor to show intracranial activity against ROS1-driven CNS metastases, as intracranial response rates observed in patients with CNS metastases at baseline were of a similar magnitude to the systemic response. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), in patients with CNS metastases at baseline and measurable disease, IC-ORR was [redacted]%, IC-DOR among responders was [redacted] months, and median IC-PFS was [redacted] months. Data at the time of the second integrated efficacy analysis (CCOD of 30 October 2018), was similar to those observed in the primary integrated efficacy analysis.

Entrectinib appears to be a more effective ROS1-targeted treatment than crizotinib. Entrectinib improved OS and significantly increased the ORR compared to crizotinib (PROFILE 1001) in an ITC. There are currently no other ROS1-targeted treatments available in the UK and the only other treatment option for ROS1-positive patients is non-targeted chemotherapy. It is well accepted that ROS1-targeted treatment is superior to non-targeted chemotherapy with regard to clinical effectiveness. This was observed in the ITC of entrectinib versus pemetrexed plus platinum with platinum maintenance (ASCEND-4) across OS, PFS and ORR analyses. It has also been

directly observed in the ALK-positive NSCLC first-line setting with data from PROFILE 1014 demonstrating a 65% reduction in risk of death with ROS1-targeted treatment (crizotinib) versus pemetrexed plus platinum chemotherapy (adjusted HR: 0.35 [95% bootstrap CI: 0.08, 0.72]).[65] If entrectinib is made available in NHS England, it will further help the move towards personalised medicine in healthcare.

Entrectinib demonstrated trends towards improvements in HRQL of adult ROS1 positive advance NSCLC patients. In the STARTRK-2 study, entrectinib treatment did not detrimentally impact disease-specific HRQL. There were trends towards clinical improvement in physical and role functioning and immediate clinical meaningful improvement in the impact of physical symptoms of disease for patients treated with entrectinib. To date, entrectinib is the only ROS1 inhibitor that has demonstrated trends towards improvement in HRQL using a disease-specific instrument directly within a clinical trial.

Entrectinib is a tolerable therapy with a manageable and reversible safety profile. Overall, the type and severity of the AEs reported in the ROS1 safety population were generally consistent with their underlying disease or have been previously observed with entrectinib use in clinical trials and manageable with dose modifications. Entrectinib treatment discontinuation rates due to AEs were low ([redacted]%), and importantly, no deaths related to entrectinib treatment were observed. Although no differences in discontinuations due to AEs were observed in the ITC analyses of entrectinib versus crizotinib or pemetrexed plus platinum with platinum maintenance (see Section B.2.9), differences are observed in common AEs that suggest entrectinib could offer a favourable safety profile to patients. Of particular note are the reduced rates of visual disorders, bradycardia, gastrointestinal disorders and myelosuppression (see Section B.2.10).

Internal validity

The ROS1-positive NSCLC integrated analysis was conducted according to a formal statistical analysis plan and designed to provide as robust a dataset as possible at this time for this ultra-rare condition with significant unmet need. Recognising the particular need in patients with CNS metastases, the integrated analyses included pre-specified subgroup analyses based on the presence of CNS metastases and intracranial effect outcomes in patients confirmed to have CNS metastases by BICR.

The overall risk of bias was considered to be low in the context of the single-arm and pooled nature of the integrated analyses. However, there were some data limitations, notably a low number of events for survival outcomes (censoring was required for [redacted]% of patients in the entrectinib integrated analyses), meaning median time to event is not reached. A limitation of the ROS1-positive NSCLC integrated analysis is that it does not provide head-to-head data with alternative ROS1 treatments; this is reflective of the treatment landscape at the time of trial design as crizotinib was only approved after the three trials included in the integrated analyses had started, and conducting an randomised controlled trial (RCT) against chemotherapy would be considered unethical in this patient population. In the absence of head-to-head trial data, an ITC analysis, in accordance with NICE technical support guidance, has been conducted to provide an estimate of entrectinib compared with crizotinib and pemetrexed plus platinum with platinum maintenance. However, due to the paucity of evidence in the ROS1 population, results in ALK-positive NSCLC patients had to be used as a proxy in the comparative efficacy analyses to chemotherapy. While acceptable in consideration of the fact ALK-positive and ROS1-positive NSCLC are similar in terms of patient demographics and clinical characteristics,[16, 22] this is a clear limitation that needs considering when interpreting ITC outcomes. Nonetheless, the outcomes suggest that entrectinib offers clinical effectiveness benefit beyond that of current treatments, and this expectation is supported in the clinical community.[2, 3, 66]

In recognition of the uncertainty within the current evidence base for entrectinib in ROS1-positive NSCLC patients, and the immaturity of data from the ROS1-positive integrated analyses, an application for entrectinib as a CDF candidate is being submitted. Reimbursement of entrectinib through the CDF will enable earlier access to patients, addressing the unmet medical need, but also providing a large enough dataset to clarify uncertainties currently observed in the longer-term outcomes data, and comparative data presented.

External validity

The clinical development program for entrectinib in ROS1-positive NSCLC included data from three trials, which were conducted in 95 centres in 15 countries. As of April 2018, six ROS1-positive patients were enrolled via two of the three sites in the UK.

As described in Section B.2.3, to be included in the integrated analysis, patient's tumour samples were confirmed to be ROS1-positive using a nucleic acid-based diagnostic testing method. These methods are reflective of UK ROS1 testing strategies covered in the 2019/2020 National Genomic Test Directory for Cancer.[4]

The small ROS1-positive patient numbers included in the integrated analyses represents the rarity of ROS1-positive NSCLC. As such, there are limited UK specific demographic data for ROS1-positive NSCLC patients. However, according to UK clinical consultation, the characteristics of patients included in the ROS1-positive NSCLC integrated analyses are generally representative of the relevant patient population in UK clinical practice (e.g. younger patients, many of whom have never smoked), but noted the male:female split is closer to 50:50 in practice.[3]

Both treatment naive and treatment-experienced ROS1-positive NSCLC patients were included in the integrated analyses. While entrectinib is expected to be used in the first-line setting, it may also be used as a second-line treatment. Therefore, both treatment naive and treatment-experienced ROS1-positive NSCLC patients could be treated with entrectinib in clinical practice.

As described in Section B.1.3, it has been previously assumed that the ROS1-positive population is similar to the ALK-positive population. As such due to the paucity of evidence in the ROS1-positive NSCLC population, evidence for the ALK-positive NSCLC population has been used as a proxy for chemotherapy comparator treatments. The validity of using data from ALK clinical trials, is dependent on the ability to assume that the two biologically similar but distinct subtypes of NSCLC are comparable. This is plausible due to the fact ALK-positive and ROS1-positive NSCLC are similar in terms of patient demographics (e.g. younger age, non-smoker or light smoking) and clinical characteristics (e.g. adenocarcinoma histologic type),[16, 22] and clinical consultation endorsed the approach taken in consideration of the data limitations.[3]

The primary efficacy endpoints in the ROS1-positive NSCLC integrated analysis were ORR (including BOR) and DoR as assessed by BICR. The main aim of treatment for advanced NSCLC is to control the cancer for as long as possible and help to reduce symptoms.[67] Therefore, ORR and DoR are considered appropriate

primary endpoints, and have also been accepted and used in other clinical studies, and regulatory approval for the ROS1-positive NSCLC. Sensitivity analyses were also conducted to assess ORR and DoR by the investigator. IA is also consistent with clinical practice in NHS England. Other secondary efficacy endpoints including PFS and OS, provide data for further outcomes considered of relevance to the scope of this appraisal by expert commentators and consultees. As noted above, intracranial outcomes were also pre-specified to assess the effect of entrectinib in ROS1-positive NSCLC patients with CNS metastases – this is a patient group with no effective treatment option in current UK practice.

Although not observed in the HRQL data collected during the ROS1-positive NSCLC integrated analysis, in a real-world setting prolonging DoR and PFS is expected to have a positive impact. For example, an extended period of symptom-free disease may allow patients to return to some sort of normal living. Furthermore, increasing the patient symptom-free disease period is also likely to have significant impacts of carer quality of life.

Of final note, there is significant clinical support for the availability of entrectinib, as more selective ROS1 inhibitors are needed. In particular, clinical consultation highlighted the clear unmet need for a ROS1 targeted treatment that has both extracranial and intracranial efficacy.[3, 66]

Entrectinib as an end-of-life therapy

Evidence to support the consideration of entrectinib as an and end of life treatment in the context of NICE's end-of-life criteria are summarised in Table 34.

As can be seen from these data, without ROS1-targeted treatment, life expectancy is short and expected to fall below 24 months - this was recognised in the previous ROS1 inhibitor appraisal for ROS1-positive NSCLC with crizotinib being accepted as an end-of-life therapy in this patient population.[38] ROS-1 inhibitor therapy is expected to offer an extension to life of substantial magnitude with recent data suggesting at least a doubling of overall life expectancy (Table 34).

Table 34: End-of-life criteria

Criterion	Data available	Reference in submission/reference
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS in patients with ROS1-positive NSCLC not treated with ROS1-targeted treatment in Korean clinical practice was 20.0 months.[25]	Section B.1.3 Page 13
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed-based chemotherapy in clinical trials ranges from 19.2 to 27.7 months across treatment settings (first- to third-line plus) but it should be noted that some patients went onto receive ROS1-targeted treatment post progression.[50, 65, 68-70]	Appendix D.6 Page 92
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed plus platinum with pemetrexed maintenance in the first-line setting was 26.2 months in ASCEND-4 but this was not adjusted for crossover (43% of patients switched to ROS1-targeted treatment post progression).[50]	Section B.2.9 Page 67
	Median OS in patients with ALK-positive NSCLC who did not receive crizotinib in PROFILE 1001 was 20.0 months.	Shaw et al. 2011[71]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in the entrectinib integrated analysis, with only [redacted]% of patients having died at the time of the latest analysis (30 Oct 2018) when the minimum follow-up was [redacted] months (median follow-up 20.6 months).[43, 45]	Section B.2.6 Page 44
	Median OS associated with crizotinib was 51.4 months in PROFILE 1001. KM plots of OS in MAIC estimate a survival advantage in favour of entrectinib versus crizotinib.[48]	Section B.2.9 Page 59
	Estimated LYG with entrectinib versus pemetrexed plus platinum with pemetrexed maintenance in the economic modelling is 4.49 years (base case).	Section B.3.7 Page 164
Key: KM, Kaplan Meier; LYG, life years gained; NSCLC, non-small cell lung cancer; OS, overall survival.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

Full details of the systematic review for health-related quality-of-life data are reported in Appendix G. No published economic studies were identified which considered the cost-effectiveness of interventions for the management of patients with ROS1-positive locally advanced or metastatic NSCLC. This is consistent with the findings of the economic evaluation SLR conducted to support the submission for crizotinib to NICE for the treatment of patients with ROS1-positive advanced NSCLC (TA529).[38]

Three health technology assessment (HTA) submission documents were identified which were eligible for inclusion in the review. Two documents related to a submission and subsequent resubmission to the Pharmaceutical Benefits Advisory Committee (PBAC) for crizotinib in locally advanced or metastatic ROS1-positive NSCLC (original submission, November 2017 and resubmission, July 2018). The remaining document was a submission to NICE which considered the cost-effectiveness of crizotinib for the treatment of ROS1-positive advanced NSCLC (TA529). [38] A summary is provided in Table 35.

Table 35: Summary of identified HTA submissions

Study, country, study design	Population	Interventions and comparators	Model summary	Study perspective	Discounting	Time horizon	Model inputs (clinical, costs, QOL)
NICE TA529 UK CUA	Patients with advanced ROS1-positive NSCLC in two settings: Patients who have received no prior therapy (first-line) Patients who have received ≥1 prior therapies (subsequent-line)	First-line: Crizotinib Pemetrexed + platinum-chemotherapy Subsequent-line: Crizotinib Docetaxel	First- and subsequent-lines: Partitioned survival analysis with 30-day cycle length: Progression free Progressed Death	First- and subsequent-lines: payer (UK NHS and PSS)	First- and subsequent-lines: 3.5% costs and outcomes	First- and subsequent-lines: 20 years	Clinical: PROFILE 1001, 1007, and 1014 trials Costs: drug costs from MIMS and eMIT, NHS reference costs (administration, monitoring and AEs), PSSRU QOL: EQ-5D utilities derived from PROFILE 1014 and 1007 and from the published literature
PBAC crizotinib original submission Australia CUA	Patients with locally advanced (stage IIIB) or metastatic (stage IV) ROS1-positive NSCLC who had disease progression on or following treatment with a	ROS1 testing + crizotinib No ROS1 testing + pemetrexed	Testing phase: Decision analytic model¥ Treatment phase: Partitioned survival state-transition	NR	NR	10 years	Clinical: two single-arm studies of crizotinib in second-line treatment of NSCLC (PROFILE 1001 and OO12-01) and the pemetrexed arm of a single RCT comparing

Study, country, study design	Population	Interventions and comparators	Model summary	Study perspective	Discounting	Time horizon	Model inputs (clinical, costs, QOL)
	platinum-based chemotherapy		model with 8-week cycle length: Pre-progression Post-progression Death				pemetrexed with docetaxel for second-line treatment of NSCLC Costs: NR QOL: EORTC-QLQ-C30 data from OO12-01 trial were mapped to EQ-5D-5L utilities
PBAC crizotinib resubmission Australia CUA	Patients with locally advanced (stage IIIB) or metastatic (stage IV) ROS1-positive NSCLC (agnostic line of therapy)	ROS1 testing + crizotinib No ROS1 testing + pemetrexed	The minor resubmission did no alter the economic model structure from the original submission but sought to re-specify the best estimate of the base case ICER	NR	NR	5 years	Clinical: two single-arm studies of crizotinib in second-line treatment of NSCLC (PROFILE 1001 and OO12-01) and the pemetrexed arm of a single RCT comparing pemetrexed with docetaxel for second-line treatment of NSCLC Costs: NR

Study, country, study design	Population	Interventions and comparators	Model summary	Study perspective	Discounting	Time horizon	Model inputs (clinical, costs, QOL)
							QOL: NR

Keys: AE, adverse event; CUA, cost-utility analysis; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer QoL Questionnaire; EQ-5D(-5L), European QoL-5 Dimensions (5 Level version); FISH, fluorescence in situ hybridisation; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; NSCLC, non-small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QOL, QoL; RCT, randomised controlled trial; ROS1, ROS proto-oncogene 1; UK, United Kingdom.
¥ Used to determine the proportion of patients who would qualify for crizotinib treatment on the basis of the underlying prevalence of ROS1 positivity (estimated at 1.61%) and the analytical performance of IHC (95.1% sensitivity and 93.8% specificity) as a pre-test with FISH confirmation (100% sensitivity and specificity).

B.3.2. Economic analysis

Patient population

In line with the final scope of this appraisal and the European Marketing authorisation (EMA), the patient population for the economic model is adult patients with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer. This corresponds to the patient population in ALKA and STARTRK-1/2 for entrectinib.

Due to the small number of patients in the ALKA and STARTRK-1/2 clinical trials (n=53), an integrated analysis of efficacy was conducted across the three studies. The analysis was based on the ROS1-positive primary efficacy set, which consists of adults patients with ROS1-positive NSCLC with measurable disease at baseline and at least 12-months follow-up from the time of follow-up from the time of first response. In order to maximise the patient numbers and robustness of the analysis an “all-lines” approach has been undertaken in the economic model using the integrated analysis. This is further discussed in detail in section B.3.3 and B.2.4.

Model structure

The cost-effectiveness model was developed in Microsoft Excel®**.** The model is a partitioned survival model based on three health states (as shown in Figure 11): progression-free, progressed disease and dead.

All patients enter the model in the progression-free state and are at risk of progression or death. Transitions to the death state can occur from either the progression-free or progressed disease health states, where death is an “absorbing state”. The progression-free health state is designed to capture the relatively higher QoL, whilst the disease is controlled prior to progression, where patients are receiving benefit from an active treatment. The progressed disease state is designed to capture the relatively poor QoL following disease progression and prior to death. The model therefore captures the changes in QoL between pre- and post-progression.

The model structure is fully aligned with two of the primary objectives of treatment in NSCLC; avoiding disease progression and prolonging life. The model structure and health states selected are typical of modelling in oncology and were used in the

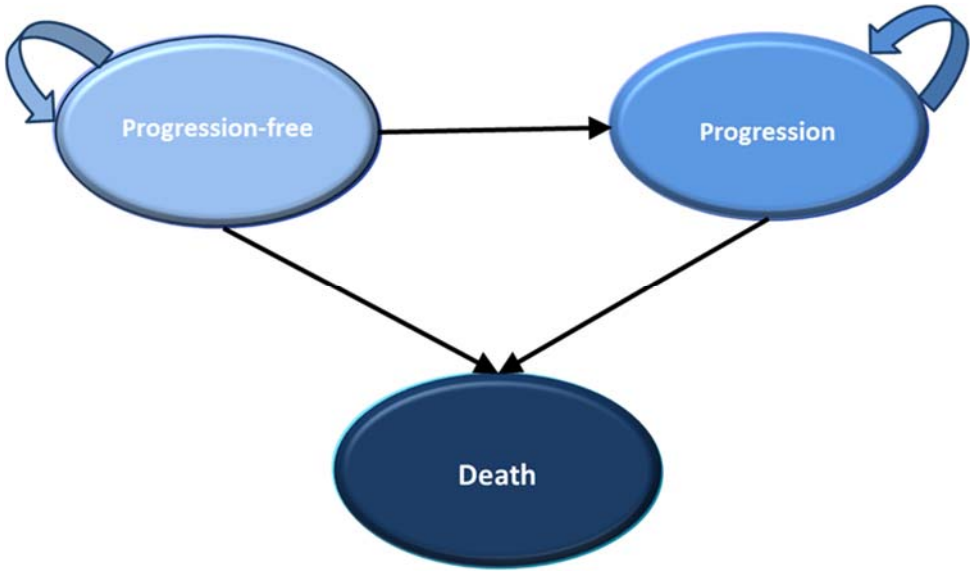
previous ROS1-positive NSCLC[38] technology appraisal, in addition to other NSCLC NICE technology appraisals.[1, 38, 39, 72-75] It contains the three most relevant disease related health states from a patient, clinician and NHS perspective:

Progression free: Patients disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, administration, medical management of the condition and the management of Grade 3/4 adverse events. Patients also experience a higher utility compared with progressed disease (based on observed utilities in the STARTRK-2 trial).[42]

Progressed: Patient's disease is assumed to have progressed and patients assumed to have moved onto subsequent treatment. This health state is associated with acquisition and administration costs of subsequent therapies as well as costs of management. The health state is also associated with a lower QoL.

Death: This is an absorbing state. A cost of palliative care is assumed upon death.

Figure 11: Model diagram



Feature of the de novo analysis

The analyses were conducted from the NHS and personal social services (PSS) perspective in England and Wales. The model uses a 30-day cycle length, with a

half-cycle correction applied and a time horizon of 30 years. This aligns with the maximum life expectancy of the cohort predicted by parametric survival analysis and, clinically, it is unlikely for patients with ROS1-positive advanced NSCLC to survive beyond 30 years. The impact of the selection of the time horizon on results is explored in sensitivity analysis. A discount rate of 3.5% per annum was applied for costs and benefits. The perspective chosen, time horizon assessed, and the discount rates used are all in line with the NICE reference case.[76]

There has been one prior NICE technology appraisal for the treatment of ROS1-positive NSCLC (TA529)[38] which is considered as a relevant comparative precedent.[38] The features of the *de novo* analysis compared with the features of TA529 are reported in Table 36.

Table 36: Features of the economic analysis and comparison with the economic analysis for crizotinib as a treatment for ROS1- positive NSCLC

Factor	Previous appraisals	Current appraisal	
	TA529	Chosen values	Justification
Time horizon	20	30	The 30 years is considered adequately long that the majority of patients would have died by the end of the model time horizon and so the model is able to reflect all differences in costs and outcomes in line with the NICE reference case[76]
Cycle length and half cycle correction	30 days (with half cycle correction applied)	30 days (with half cycle correction applied)	Based on clinical trial measurement points and pack size for entrectinib and crizotinib (30 days). For chemotherapies with cycle length of 21 days, costs were adjusted to account for the difference in treatment cycle length compared with the model cycle length.
Health states	Progression-free, progressed and death	Progression-free, progressed and death	Reflects the aim of the treatment namely maintaining patients in the progression-free state while avoiding progression and prolonging life.
Comparator	Pemetrexed plus platinum chemotherapy for first line and docetaxel monotherapy for subsequent lines of treatment.	Pemetrexed plus platinum (base case) and crizotinib (key scenario analysis)	In line with the current clinical practice in NHS England and the March 2019 published NICE guideline on lung cancer diagnosis and management [NG122].[77]
Source of utilities	PROFILE 1014 PROFILE 1007 Nafees et al. (2008)[78]	STARTRK-2, PROFILE 1007	Utility values were derived from EQ-5D data collected in STARTRK 2; in line with the NICE reference case. Where not available, EQ-5D data were sourced from TA529[38] and relevant literatures, in line with the NICE reference case.

Factor	Previous appraisals	Current appraisal	
	TA529	Chosen values	Justification
Source of costs	**Drug costs:** MIMS[79] and eMIT (generic)[80] **Other costs:** NHS reference costs (administration, monitoring and adverse event costs) PSSRU (administration, monitoring and palliative care costs) [81, 82]	**Drug costs:** MIMS[79] and eMIT (generic)[80] **Other costs:** NHS reference costs (administration, monitoring and adverse event costs) PSSRU (administration, monitoring and palliative care costs)[81, 82]	**Drug costs:** The public list price of the treatments should be used, in line with the NICE reference case.[76] **Other costs:** Consistent with NICE reference case (resources should be valued using the prices relevant to the NHS).
Half cycle correction applied?	Yes	Yes	Consistent with NICE reference case [76]
Health effects measure	QALYs	QALYs	Consistent with NICE reference case [76]
Discount rates	3.5%	3.5%	Consistent with NICE reference case [76]
Perspective	NHS/PSS	NHS/PSS	Consistent with the NICE reference case [76]

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE; National Institute for Health Care and Excellence; NSCLC, non-small cell lung cancer; PSS, Prescribed Specialised Services; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; TA, technology appraisal.

Intervention

Entrectinib (also known as RXDX-101) is a single oral tyrosine kinase inhibitor chemotherapy, recommended at a daily dose of 600mg in repeated 30-day cycles. The anticipated licence for entrectinib is adult patients with ROS1 fusion-positive locally advanced or metastatic NSCLC.

According to the summary of Product characteristics,[5] entrectinib was administrated until disease progression or clinical deterioration in the clinical trials (ALKA and STARTRK-1/2). Time on treatment (ToT) data from ALKA[40] and STARTRK-1/2[41, 42] for entrectinib were used in the base case to estimate the cost of entrectinib. The method used to account for ToT is aligned with the accepted modelling approach used in the crizotinib submission.[38]

Comparators

Section B.1.3 details the current NHS clinical pathway for treating ROS1-positive NSCLC patients and Section B.1.1 discusses the relevant comparators for the submission compared to the final scope, but key points are reiterated here.

Following confirmation of ROS1-positive status, crizotinib is recommended as a first-line treatment, and is preferred to chemotherapy for all ROS1-positive NSCLC patients in current clinical practice.[1-3] However, crizotinib is funded through the CDF and therefore not typically considered an appropriate comparator within the technology appraisal scoping process according to the recent NICE position statement.

Prior to crizotinib funding through the CDF, pemetrexed plus platinum was considered standard of care for ROS1-positive NSCLC patients, and this was considered the relevant comparator in the first-line setting within the crizotinib appraisal (TA529).[38] Pemetrexed plus platinum is now recommended in the second-line setting.[1]

Following advice received from the NICE technical team the comparators considered in the economic model are therefore pemetrexed plus platinum in the base case and crizotinib in a key scenario. This approach allows for consistent decision making

across ROS1-inhibitor appraisals while acknowledging current clinical practice, and the application for funding through the CDF for entrectinib.

Given the small size of patients in the ALKA and STARTRK-1/2 clinical trials, it was not possible to differentiate between naïve and previously treated patients and so an "all-lines" approach has been used in this appraisal in order to maximise the patient numbers and robustness of the available data. Comparators are however based on the intended use of entrectinib in the first- or second-line setting, with later-line treatments considered as part of subsequent therapy but not as direct comparators of relevance to this appraisal.

B.3.3. Clinical parameters and variables

B.3.3.1 Clinical data incorporated into the model

Efficacy inputs, including PFS, OS and ToT for the entrectinib arm were based on the integrated analysis conducted across the three entrectinib studies (ALKA, STARTRK-1 and STARTRK-2) for ROS-1 positive patients.

Given the lack of comparative data from the entrectinib ROS1-positive clinical trials, an indirect treatment comparison is required to demonstrate the relative treatment effect of entrectinib compared to pemetrexed plus platinum and crizotinib. The limited availability of comparator data in ROS1-positive NSCLC patients means there is uncertainty regarding the comparative efficacy of entrectinib versus both crizotinib and pemetrexed plus platinum and therefore alternative options have been included in the economic model.

As we are proactively targeting a CDF recommendation, a comparison to crizotinib has been made in a key scenario analysis as crizotinib is assumed to be the most clinically relevant comparator. It was suggested by the clinical expert at the clinical validation meeting that upon ROS1 status confirmation, patients will receive crizotinib as a standard of care rather than chemotherapy regimens.[3] OS and PFS for crizotinib were estimated from a MAIC of the integrated analysis of efficacy conducted across the three entrectinib trials to the patient population in PROFILE 1001. [83] Details on the MAIC methods and assumptions are described in Section B.2.9 and Appendix D.

In the base case comparison to pemetrexed plus platinum, efficacy inputs for pemetrexed plus platinum were based on the published HR from PROFILE 1014 and applied to the modelled crizotinib arm. This HR was previously used and accepted for ROS1-positive NSCLC patients in TA529.

AEs data from the integrated analysis (ALKA and STARTRK-1/2), PROFILE 1014 [65]and PROFILE 1001[83] were used to estimate the proportion of patients experiencing treatment-related Grade 3/4 AEs in the entrectinib, pemetrexed plus platinum and crizotinib arms, respectively.

Important patient characteristics such as age, height and weight were sourced from the integrated analysis of the entrectinib trials (ALKA and STARTRK-1/2). As such, BSA was calculated using the reported height and weight using the DuBois Formula.[84] The resulting BSA of 1.78m^2 is closely aligned to that reported in PROFILE 1001 (1.80m^2). [83]

B.3.3.2 Extrapolation of data

Overall survival

Entrectinib

Overall survival for the entrectinib arm were estimated using the ROS1-positive data from the integrated analysis. Treatment efficacy beyond the trial follow-up period was derived by fitting parametric survival curves to the OS KM data. Survival curve fitting was conducted in line with the NICE DSU TSD 14.[85] All standard parametric models were considered and compared. These included; exponential, Weibull, log-normal, log-logistic, Gompertz and gamma. The fit of the alternative models was assessed by:

- Comparing both the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC), where the model with the lowest AIC/BIC indicates the best statistically fitting curve.
- Performing a visual inspection of the fitted curves.
- Assessing clinical expert opinion on the plausibility of long-term clinical outcomes and expected survival from other data sources.

The AIC/BIC statistics for the entrectinib OS curves are reported in Table 37. The OS curve fits, alongside the KM curves are presented in Figure 12.

According to the AIC/BIC statistics all curves has a similar statistical fit to the data. The exponential curve was deemed as the most appropriate base case curve for OS as it provided the most conservative estimates (Figure 13). This was considered the most clinically plausible OS estimate for entrectinib by the clinical expert consulted as part of the validation of the curves.[3] The exponential curve was considered to be the most appropriate curve for OS in TA529.[58]

Although the exponential curve was considered to be the most clinically plausible estimate by the clinical expert, it was considered that the long-term extrapolations were probably optimistic when you take into consideration the development of resistance which would affect the tail of the curve. [3] The overestimation in the predicted OS is due to the small patient numbers in the ALKA and STARTRK-1/2 clinical trials. As such, alternative curves options are explored in the scenario analysis.

Figure 12: Visual fit of the OS parametric functions to the entrectinib ROS1 integrated data

Figure 13: Selected curve to the entrectinib ROS1-positive OS integrated data

Table 37: AIC and BIC for entrectinib OS

Model	AIC	BIC
Exponential	101.00	102.90
Weibull	102.80	106.70
Log-normal	101.60	105.60
Gamma	102.40	108.30
Log-logistic	102.40	106.40
Gompertz	101.80	105.70
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.		

Crizotinib

In the key scenario analyses where crizotinib is considered as the relevant comparator, the OS for patients in the crizotinib arm was estimated by a MAIC between the integrated analysis conducted across the three entrectinib studies and the crizotinib arm from PROFILE 1001 using data cut-off of May 2014.[47] Details regarding the method employed for the MAIC are presented in Section B.2.9. and

Appendix D. The inverse of the estimated HR from the MAIC ([redacted] [95% CI: [redacted])]) was applied to the modelled entrectinib OS curve to estimate OS for crizotinib. The resulting OS curve for crizotinib, used in the model, is presented in Figure 14.

The PROFILE 1001 study was considered as the most appropriate evidence as it is the only study that specifically included ROS1-positive NSCLC patients receiving crizotinib. The use of the MAIC over a simple naïve comparison versus crizotinib was considered as the best approach as it adjusts for any differences in patient characteristics between the entrectinib trials and the PROFILE 1001 trial. A limitation for the approach is that the small sample size limits the number of variables which can be used in matching, as matching weights can quickly become over specified if many variables are included. The high uncertainty in the MAIC results, demonstrated by the width of the 95% CIs, is mainly driven not only by the small sample sizes in the ROS1-positive NSCLC patient groups, but also by the low number of events.

The resulting OS curve for crizotinib was validated by a clinical expert who agreed that it was reasonable, although predicts better survival than is seen in clinical practice for patients receiving crizotinib. The clinical expert highlighted that in general, the real-world data of crizotinib shows survival to be less good than that observed in PROFILE 1001. [3] This is in line with what is seen in the real-world data from the Flatiron Health Analytic Database real world evidence (Appendix D). This showed a median OS of 18.5 months in clinical practice for ROS1-positive NSCLC patients receiving crizotinib. This is significantly lower than the median OS observed in PROFILE 1001 and the median OS predicted in the model using the HR from the MAIC.

As presented in Section B.2.9 an update to the PROFILE 1001 OS data was recently released. When reviewing these data against the modelled OS presented in Figure 14 it looks as if the modelled estimates are underestimating survival. However, given the feedback on the extrapolations (that is that they are overestimating survival), this is not considered clinically plausible, and no changes to extrapolation have been adopted on their basis.

Further to this, since the time that crizotinib was recommended as a treatment for ROS1-positive NSCLC, more advanced treatments have become available. As a result of this is it possible that patients in the ALKA and STARTRK-1/2 clinical trials may receive therapies post-progression which would be expected to be associated with better outcomes than those received in PROFILE 1001. The treatments received post-progression in PROFILE 1001 have not been reported and so it was not possible for us to explore this possibility.

Figure 14: Modelled crizotinib curve presented against the entrectinib modelled curve and KM data using HR from the MAIC – key scenario analysis

An alternative modelling approach where a naïve comparison to crizotinib OS data based on the PROFILE 1001 data was also presented in the key scenario analysis.

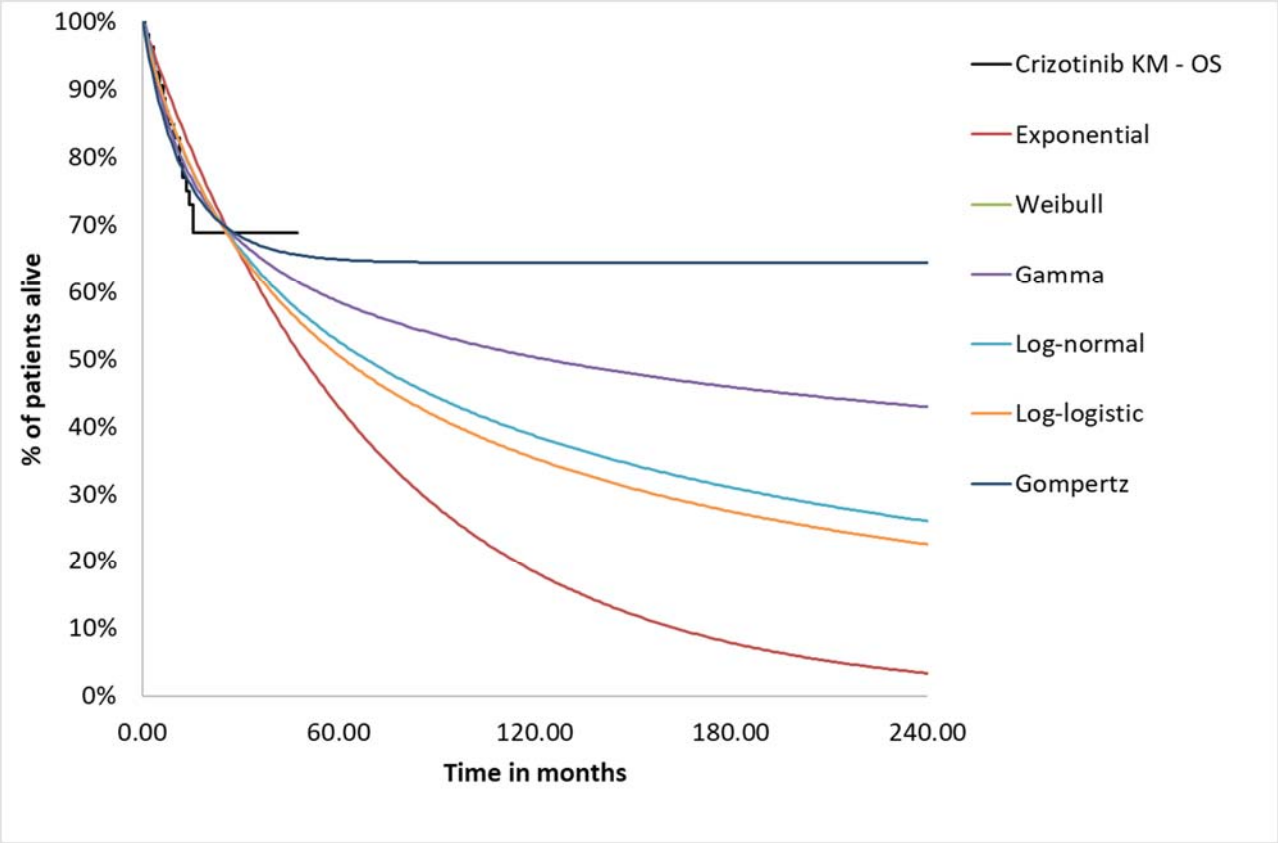
KM graphs were digitized using GetData Graph Digitizer[86] to create pseudo-IPD using the Guyot algorithm.[87] Parametric survival curves were then fitted to these pseudo-IPD data in line with the NICE DSU TSD 14.[85]

The fitted parametric curves are presented in Figure 15. Based on the AIC/BIC, the exponential and log-normal curves were the best statistically fitting curves (Table 38). However, given that the log-normal curve resulted in clinically implausible long-

term outcomes, the exponential curve was selected as the most appropriate curve with the most clinically plausible results (Figure 16). This is in line with the recommendation from NICE DSU TSD 14[85] where the same type of parametric survival curves should be chosen for all treatments when fitting independent curves.

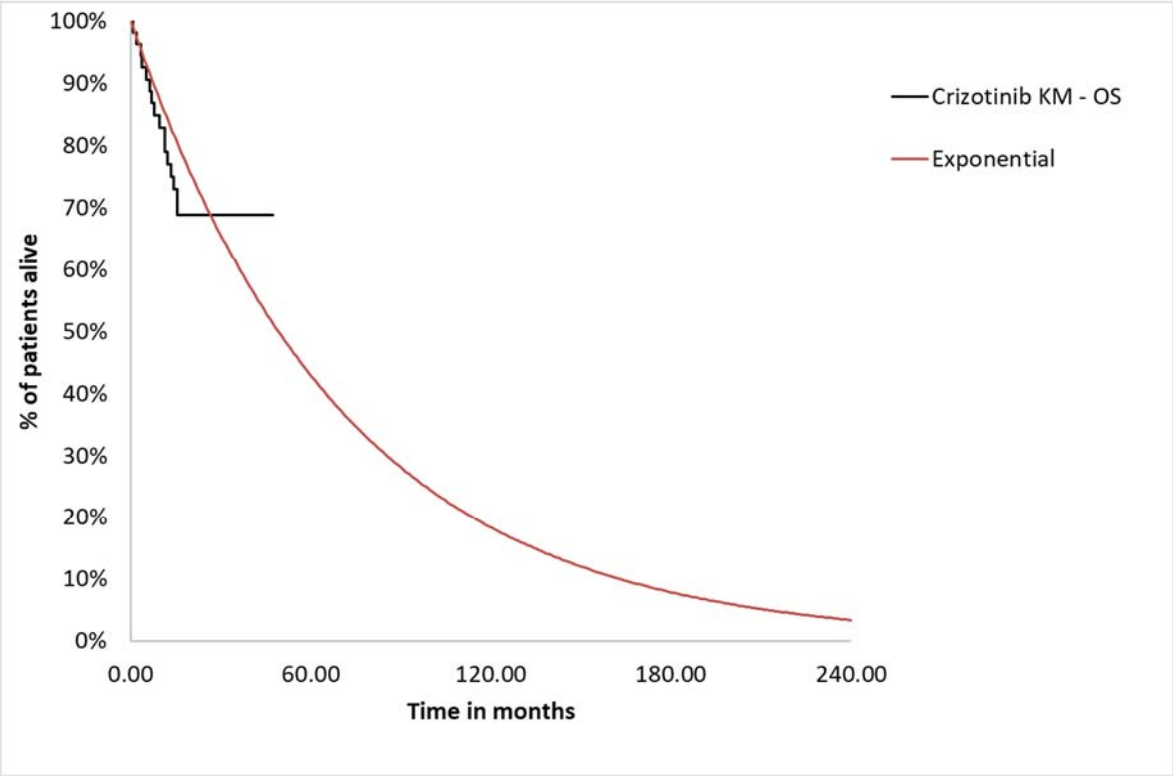
Using the OS data based on the naïve comparison to PROFILE 1001 resulted in 49.3 months median OS for crizotinib, providing a closer estimate to the reported median OS in PROFILE 1001.

Figure 15: Visual fit of the OS parametric functions to the crizotinib PROFILE 1001 ROS1-positive NSCLC data



Key: KM, Kaplan–Meier; OS, overall survival; NSCLC, non-small cell lung cancer

Figure 16: Selected curve to the crizotinib PROFILE 1001 ROS1-positive NSCLC OS data- alternative modelling approach



Key: KM, Kaplan–Meier; OS, overall survival; NSCLC, non-small cell lung cancer.

Table 38: AIC and BIC for crizotinib PROFILE 1001 OS

Model	AIC	BIC
Exponential	170.31	170.31
Weibull	171.24	175.18
Log-normal	168.82	172.76
Gamma	169.36	175.27
Log-logistic	170.17	174.11
Gompertz	167.23	171.17
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.		

Pemetrexed plus platinum

There is no data available for pemetrexed plus platinum in ROS1-positive NSCLC. In the base case in TA529, ALK-positive data was used as proxy for ROS1-positive

NSCLC in the absence of data for pemetrexed plus platinum in ROS1-positive NSCLC.

Therefore, in the model base case, the OS for patients in the pemetrexed plus platinum arm was estimated using the published HR from PROFILE 1014 and applied to the estimated crizotinib OS. PROFILE 1014 (n=171 in chemotherapy arm) is a first-line trial of crizotinib versus pemetrexed, 500mg per square meter of body-surface area, plus either cisplatin, 75mg per square meter, or carboplatin, target area under the curve of 5 to 6mg per millilitre per minute) every 3 weeks for up to six cycles.

The HR for crizotinib versus pemetrexed plus platinum was taken from the latest reported data cut from PROFILE 1014 (HR = 0.346 [95% CI: 0.081, 0.718]). The rank preserving structural failure time model (RFPSTM) was used to adjust for crossover. The inverse of this HR was then applied to the modelled crizotinib OS curve in the model to estimate the OS for pemetrexed plus platinum. The HR used was previously used and accepted for ROS1-positive NSCLC patients in TA529. The resulting OS curves is presented in Figure 17.

This approach is preferred to applying the HR of the MAIC summarised in Section B.2.9 as it is limited to the assumption of equivalence treatment effect across ROS1-positive and ALK-positive NSCLC populations. As the HR is applied to the OS curve for crizotinib in ROS1-positive NSCLC any difference in expected outcomes between ALK-positive and ROS1-positive NSCLC is already adjusted for. A limitation to this approach is the pemetrexed plus platinum arm does not include pemetrexed maintenance therapy, which may be used in clinical practice and could improve survival. However, pemetrexed maintenance is only funded after pemetrexed plus cisplatin in current practice, and it was agreed by the committee in TA529 that only a small number of patients will be eligible to receive pemetrexed maintenance therapy.

Figure 17: Modelled pemetrexed plus platinum curve presented against the entrectinib and crizotinib modelled curves – base case

An alternative scenario is presented where the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the chemotherapy arm from the ASCEND-4 trial (n=187) is used to estimate the pemetrexed plus platinum arm. In the ASCEND-4 trial, ceritinib was compared to platinum-based chemotherapy (pemetrexed plus cisplatin or carboplatin) at first-line followed by pemetrexed maintenance in ALK-positive NSCLC patients. The inverse of the estimated HR of 0.458 (95% CI: 0.140 to 0.901) from the MAIC is then applied to the modelled entrectinib OS curve estimating the OS for the chemotherapy arm illustrated in Figure 18. Further details about the MAIC are presented in Section B.2.9.

This shows a comparison to pemetrexed plus platinum with pemetrexed maintenance, however is associated with the key limitation that it requires the assumption that ROS1 versus ALK gene fusion status is not in itself either prognostic or a treatment effect modifier once imbalances in other patient characteristics have

been accounted for. In addition, data on survival outcomes in the integrated entrectinib studies are quite immature with few events observed and median overall survival not reached leading to greater uncertainty in the results.

The resulting OS curve for pemetrexed plus platinum was validated by a clinical expert who agreed that the estimated curve using the HR from the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the pemetrexed plus platinum with platinum maintenance arm from the ASCEND-4 trial resulted in an overly optimistic proportion of patients alive at 5 years (23.8%).[3] As a result, the curve estimated using the published HR applied on the estimated crizotinib arm was deemed to be more reflective of what is seen in clinical practice.

Figure 18: Modelled pemetrexed plus platinum curve presented against the entrectinib modelled curve and KM data using HR from the MAIC –scenario analysis

Progression free survival

Entrectinib

Progression-free survival for the entrectinib arm were estimated using the integrated analysis. Treatment efficacy beyond the trial follow-up period was derived by fitting parametric survival curves to the PFS KM data. Survival curve fitting was conducted in line with the NICE DSU TSD 14.[85] All standard parametric models were considered and compared. These included exponential, Weibull, log-normal, log-logistic, Gompertz and gamma. The fit of the alternative models was assessed by:

- Comparing both the AIC and BIC, where the model with the lowest AIC/BIC indicates the best statistically fitting curve.
- Performing a visual inspection of the fitted curves
- Assessing clinical expert opinion on the plausibility of long-term clinical outcomes, and expected survival from other data sources

The AIC/BIC statistics for the entrectinib PFS curves are reported in Table 39. The PFS curve fits, alongside the KM curves are presented in Figure 19.

According to the AIC/BIC statistical all curves had a similarly good statistical fit to the data. The exponential curve was deemed as the most appropriate base case curve for PFS as it provided the most clinically plausible estimates. Clinical expert opinion confirmed that the selected entrectinib PFS curve was a reasonable estimate of PFS.[3] The selection of the exponential curve is in line with the chosen and accepted PFS curve in TA529.[58] Alternative curve options are explored in the scenario analysis.

Figure 19: Visual fit of the PFS parametric functions to the entrectinib ROS1-positive integrated data

Figure 20: Selected curve to the entrectinib ROS1-positive PFS integrated data

Table 39: AIC and BIC for entrectinib PFS

Model	AIC	BIC
Exponential	214.00	216.00
Weibull	215.90	219.80
Log-normal	217.40	221.30
Gamma	216.60	222.50
Log-logistic	217.10	221.00
Gompertz	215.60	219.50
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; PS, progression-free survival		

Crizotinib

In the key scenario analyses where crizotinib is considered as a relevant comparator, the PFS for patients in the crizotinib arm was estimated by a MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the crizotinib arm from PROFILE 1001. The entrectinib clinical trials

reported PFS as either IA or assessed by blinded independent review committee (BICR). As it was unclear if PFS reported in PROFILE 1001 is IA or BICR, separate comparisons of the PFS IA and PFS BICR were performed, using the integrated entrectinib trials and the PFS data reported in PROFILE 1001. The PFS BICR was used in the base case, but PFS IA was presented as a scenario analysis. Details about the MAIC are presented in Section B.2.9.

The inverse of the estimated HR of [redacted] (95% CI: [redacted]) from the MAIC was applied to the modelled entrectinib PFS curve to estimate PFS for crizotinib. The resulting PFS curve for crizotinib, is presented in Figure 21.

The PROFILE 1001 study was considered as the most appropriate evidence as it is the only study that specifically included ROS1-positive NSCLC patients receiving crizotinib. The use of the MAIC over a simple naïve comparison versus crizotinib was considered as a more robust approach to compare two treatments as it adjusts for any differences in patient characteristics between the entrectinib trials and the PROFILE 1001 and so analyses are not biased by the differences in the patient population across trials. However, the small sample size limits the number of variables which can be used in matching, as matching weights can quickly become over specified if many variables are included. The high uncertainty in the MAIC results was demonstrated by the width of the 95% CI, which is mainly driven not only by the small sample sizes in the ROS1-positive NSCLC patient groups, but also by the low number of events.

The resulting PFS curve for crizotinib was validated by a clinical expert who agreed that the resulting PFS was reasonable, although better than would be expected in clinical practice. The clinical expert highlighted that the real-world experience of crizotinib did not match PROFILE 1001 outcomes, and that the PFS seen in clinical practice is much shorter. [3]

Figure 21: Modelled crizotinib curve presented against the entrectinib modelled curve and KM data using HR from the MAIC- key scenario (PFS BICR)

In the second approach where the PFS IA is used, the HR of [redacted] (95% CI: [redacted]) for entrectinib versus crizotinib based on MAIC suggests that treatment with entrectinib is associated with a significantly higher risk of disease progression relative to crizotinib. This is reflected in the shorter median PFS for patients treated with entrectinib compared to those receiving crizotinib. There was high uncertainty in the MAIC results as demonstrated by the width of the 95% CIs. This is driven not only by the small sample sizes in the ROS1-positive NSCLC patient groups, but also by the low number of events. The resulting curves are shown in Figure 22. These data lack face validity and are not supported with real-world studies that report median PFS data ranging from 5.5 to 15 months with crizotinib use in clinical practice. [20, 35, 38, 55-57]

Applying these data in the model also suggest there is a large post-progression survival benefit with entrectinib versus crizotinib which is not in line with clinical expectations. Entrectinib is a more potent inhibitor of ROS1 than crizotinib and has shown both intracranial and extracranial activity in the clinical trial programme (see Section B.2.7). This would be expected to translate to both a PFS and an OS benefit in clinical practice. Such a benefit is observed in the alternative ITC using Flatiron data of ROS1-positive NSCLC patients receiving crizotinib treatment in US real world practice that reported a significantly lower risk of disease progression (PFS HR: 0.44 [95% CI: 0.26, 0.75]) with entrectinib. Full details of this analysis and further ITC analyses using Flatiron data are provided in Appendix D.

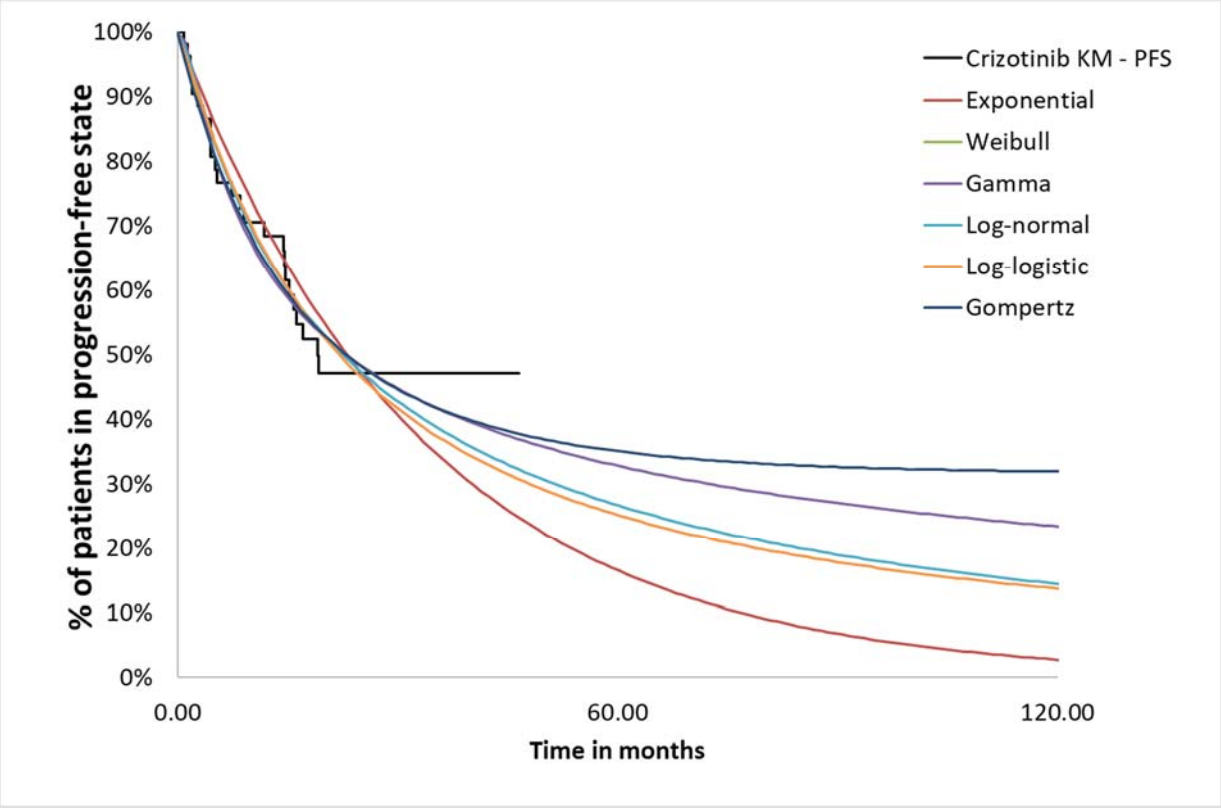
Figure 22: Modelled crizotinib curve presented against the entrectinib modelled curve and KM data using HR from the MAIC- alternative approach (PFS IA)

An alternative modelling approach where a naïve comparison to crizotinib PFS data based on the PROFILE 1001 data presented in TA529 was presented in the key scenario analysis to demonstrate the impact of the MAIC.[38]

KM graphs were digitized using GetData Graph Digitizer[86] to create pseudo-IPD using the Guyot algorithm.[87] Parametric survival curves were then fitted to these pseudo-IPD data in line with the NICE DSU TSD 14.[85]

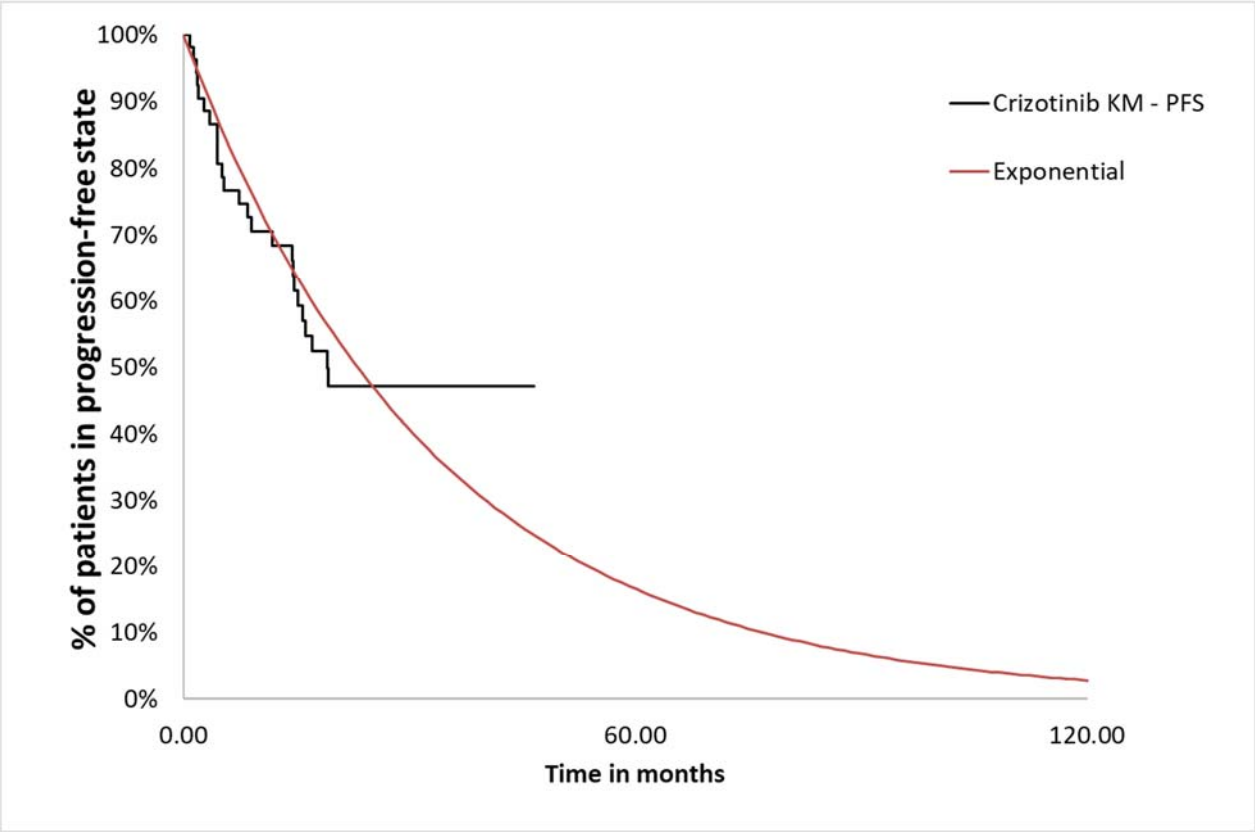
Based on the AIC/BIC, the log-normal curve was the best fitted curve (Table 40 Table 38). However, given that the log-normal curve resulted in clinically implausible long-term outcomes, the exponential curve was selected as the most appropriate curve with the most clinically plausible results (Figure 23 and Figure 24). This is in line with the recommendation from NICE DSU TSD 14[85] where the same type of parametric survival curves should be chosen for all treatments when fitting independent curves.

Figure 23: Visual fit of the PFS parametric functions to the crizotinib PROFILE 1001 ROS1 data



Key: KM, Kaplan–Meier; PFS, progression free survival.

Figure 24: Selected curve to the crizotinib PROFILE 1001 ROS1-positive OS data- alternative approach



Key: KM, Kaplan–Meier; PFS, progression free survival.

Table 40: AIC and BIC for crizotinib PROFILE 1001 PFS

Model	AIC	BIC
Exponential	236.32	236.32
Weibull	235.30	241.21
Log-normal	235.15	239.09
Gamma	235.63	239.57
Log-logistic	234.33	238.27
Gompertz	237.69	241.63
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.		

Pemetrexed plus platinum

In the model base case where pemetrexed plus platinum is considered as the only relevant comparator, the PFS for patients in the pemetrexed plus platinum arm was

estimated using the published HR from PROFILE 1014 and applied to the estimated crizotinib arm described in the later section. The resulting HR of 0.45 (95% CI: 0.35–0.60) resulted in the curve presented in Figure 25. Using this approach, the median PFS of 7.89 was estimated for the pemetrexed plus platinum which is in line with reported median PFS of 7 months in the PROFILE 1014. This approach was preferred over applying the HR of the MAIC for the same reasons described for the approach to OS modelling for this comparison.

Figure 25: Modelled pemetrexed curve presented against the entrectinib and crizotinib modelled curves along with the entrectinib PFS KM data using published HR from PROFILE 1014 – base case

An alternative scenario is presented where the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the chemotherapy arm from the ASCEND-4 trial is used to estimate the pemetrexed plus platinum arm. The estimated HR of [redacted] (95% CI: [redacted]) from the MAIC is then applied to the modelled entrectinib PFS curve estimating the PFS for the chemotherapy arm illustrated in Figure 26. The MAIC shows that treatment with

entrectinib significantly reduced the risk of progression, a result of the longer PFS (19 months compared to 8 months).

Further details about the MAIC are presented in Section B.2.9.

Although the estimated PFS curve using the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the pemetrexed plus platinum with pemetrexed maintenance arm from the ASCEND-4 trial was considered as clinically plausible by the clinical expert and shows a comparison to pemetrexed plus platinum-therapy followed by maintenance therapy, the published HR from PROFILE 1014 was used in the base case on the basis of the following rationales:

- Firstly, it is important that the source of the OS and PFS of the same treatment arm are aligned
- Secondly, the key limitation in using this alternative scenario is that it requires the assumption that ROS1 versus ALK rearrangement status is not in itself either prognostic or a treatment effect modifier once imbalances in other patient characteristics have been accounted for

Figure 26: Modelled pemetrexed plus platinum curve presented against the entrectinib modelled curve and KM data using HR from the MAIC – scenario analysis

Modelling time on treatment

Entrectinib

ToT for the entrectinib arm was estimated using the integrated ROS1-positive NSCLC trial data from the ALKA and STARTRK-1/2 clinical trials. Extrapolation beyond the trial follow-up period was performed by fitting parametric survival curves to the ToT KM data. Survival curve fitting was conducted in line with the NICE DSU TSD 14.[85] All standard parametric models were considered and compared. These included exponentials, Weibull, log-normal, log-logistic and Gompertz. However, the gamma curve was dismissed as it failed to converge.

The fit of the models was assessed by:

- Comparing both the AIC and BIC, where the model with the lowest AIC/BIC indicates the best statistically fitting curve.
- Performing a visual inspection of the fitted curves
- Assessing the expert opinion on the plausibility of the predicted drug's clinical use within the NHS clinical setting.

The AIC/BIC statistics for the entrectinib ToT curves are show in Table 41. The ToT curve fits, alongside the KM curves are presented in Figure 27.

Using the above criteria, the exponential curve was deemed as the most appropriate base case curve for ToT as it provided the most clinically plausible estimates according to the clinical expert (Figure 28). [3] Alternative curves options are explored in the scenario analysis.

Figure 27: Visual fit of the ToT parametric functions to the entrectinib ROS1-positive integrated data

Figure 28: Selected curve to the entrectinib ROS1-positive ToT integrated data

Key: KM, Kaplan–Meier; ToT, time on treatment.

Table 41: AIC and BIC for entrectinib TOT

Model	AIC	BIC
Exponential	268.70	270.70
Weibull	270.00	274.00
Log-normal	276.40	280.30
Log-logistic	274.30	278.20
Gompertz	270.20	274.20
Gamma	NC	NC

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; NC; no convergence; ToT, time on treatment.

Pemetrexed plus platinum

The SmPC for pemetrexed plus platinum allows for between 4 and 6 cycles of chemotherapy. In the base case 6 cycles of pemetrexed plus platinum is used in line with the SmPC and TA529. A sensitivity analysis is presented assuming 4 cycles of pemetrexed plus platinum are given.

Crizotinib

Due to the absence of the publicly available ToT data from PROFILE 1001, assumption is made where crizotinib is given until progression. This aligns with the assumptions made for crizotinib in ALK-positive NSCLC in TA536, where clinical opinion stated that in clinical practice crizotinib is administered until disease progression or unacceptable toxicity.[88] This is further supported by outcomes of the ALEX trial, where the observed median ToT is equivalent to median PFS.[88] As such, treatment duration and therefore drug acquisition costs for crizotinib are implemented using PFS data.

B.3.4. Measurement and valuation of health effects

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

Utility data was collected in STARTRK-2 using the EQ-5D questionnaire. The EQ-5D was scored according to its scoring manual. Each dimension of the health state profiles (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) included the proportion of patients reporting “no health problems” “moderate health problems” and “extreme health problems”. All patients completed the EQ-5D-3L questionnaires prior to any other clinical activity on Day 1 Cycle 1, Day 1 of each subsequent treatment cycle thereafter, and at the end of treatment. The UK tariff[89] was used to estimate utilities. The utilities observed in STARTRK-2 are reported in Table 42.

Table 42: Descriptive Statistics of ROS1 utilities

State	Number of Observations	Mean	Minimum	Maximum	Median
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: PFS, progression free survival; PPS, post-progression survival.					

The EQ-5D is a standardised and validated generic instrument, and the preference elicitation is based on a time trade off algorithm, which corresponds to the NICE reference case.[76]

A linear mixed model was fit to the data. Given limited observations a model was fit to the PFS observations with sex, extent (of the metastasis), age and time from treatment start investigated as fixed effects. Following a step-wise selection all fixed effects were removed. To capture the correlations between repeated assessments per patient, a random effect for intercept and slope were included as random effects in the statistical model. The final model results in a population mean estimate with 95% CI for PFS utility of 0.73 (95% CI: 0.64, 0.83).

B.3.4.2. Mapping

Mapping was not used within this economic evaluation.

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

In the base case, the utility values used to inform the pre-progression health state in the economic model were taken from the STARTRK-2 study. It is conservatively assumed that all treatment arms will have the same utility value. It is not possible to include robust post-progression utility values from the STARTRK-2 clinical trial due to the limited number of observations post-progression. Therefore, the post-progression utility values were sourced from the literature.

No publications were included in the SLR reporting utility values for ROS1-positive NSCLC. Full details of the systematic review for HRQL data are located in Appendix H.

In the base case, the post-progression utilities are assumed to be the same as those used and accepted in TA529, sourced from the PROFILE 1007 study for patients with ALK-positive NSCLC who have progressed. These were previously used and accepted for ROS1-positive patients in TA529 and so are considered the most appropriate available values, in the absence of values for ROS1-positive NSCLC patients.

A summary of the utility values used in the economic analysis is provided in Table 47.

B.3.4.4. Adverse reactions

Adverse events were shown to have a negative impact on patient's HRQL. In Doyle *et al*. (2008)[90] a standard gamble interview was conducted with 101 healthy participants with metastatic lung cancer. A mixed model analysis was used to estimate utility decrements associated with different symptoms and disease states. The study concluded that symptoms such as pain, cough and dyspnoea have a significant negative effect on patient's HRQL. In Nafees et al. (2008),[78] a standard gamble interview was also conducted with members of the general UK population where clinicians described the likely impact of adverse events at different stages of the metastatic NCSLC disease, and participants rated 12 health states. Using a mixed random effect model, it was found that all toxicities were associated with a significant decline in utility compared to stable disease with no toxicity. Table 43 illustrates adverse events utility decrements used in the cost-effectiveness model base case, sourced from Nafees *et al*.[78]

Table 43: Utility values for the anchor health states and utility decrements associated with adverse events[78]

Parameter	Utility	Parameter estimates	SE	Degrees of freedom	t-value	P-value
Intercept		0.6532	0.02223	99	29.39	<0.0001
Progressive	0.473	-0.1798	0.02169	99	-8.29	<0.0001
Response	0.673	0.0193	0.006556	99	2.94	0.004
Stable		0				
Neutropenia		-0.08973	0.01543	99	-5.82	<0.0001
Febrile neutropenia		-0.09002	0.01633	99	-5.51	<0.0001
Fatigue		-0.07346	0.01849	99	-3.97	0.0001
Diarrhoea		-0.0468	0.01553	99	-3.01	0.0033
Hair loss		-0.04495	0.01482	99	-3.03	0.0031
Rash		-0.03248	0.01171	99	-2.77	0.0066

Key: SE, standard error.

In order to capture the impact of AEs associated with treatment, a one-off QALY decrement is applied in the base case, estimated from the AEs reported in the key clinical trials and reported utility decrements from the literature. In the model base case, for the entrectinib arm Grade 3/4 treatment-related adverse events were included in the model from the integrated entrectinib trials (ALKA and STARTRK-1/2). Similarly, AEs for the crizotinib arm were sourced from PROFILE 1001 and AEs rates for the pemetrexed plus platinum were sourced from PROFILE 1014. Table 44 illustrates all AE rates used in the model base case. Table 45 reports the utility decrement and assumed duration for each AE. Durations and utility values are in line with those assumed in TA529 and have been accepted by the committee. The resulting one-off QALY decrements applied in the economic model are reported in Table 46.

Table 44: Adverse Events rates used in the model base case

Adverse events	Entrectinib arm ALKA/ STARTRK-1/2 (N=[redacted])	Crizotinib arm PROFILE 1001 (N=53)	Pemetrexed plus platinum PROFILE 1014 (N=171)
Anaemia	[redacted]	0.0%	8.9%
Arthralgia	[redacted]	0.0%	0.0%
Elevated Transaminases	[redacted]	0.0%	2.3%
Hypophosphatemia	[redacted]	13.2%	0.0%
Leukopenia	[redacted]	0.0%	5.3%
Myalgia	[redacted]	0.0%	0.0%
Neutropenia	[redacted]	9.4%	15.4%
Pulmonary embolism	[redacted]	0.0%	6.5%
Thrombocyte	[redacted]	0.0%	6.5%
Weight increased	[redacted]	0.0%	0.0%

Table 45: AEs duration and utility decrement used in the model

Adverse events	AEs duration (days)	Source	Utility decrement	Source
Anaemia	30	Assumed (in line with TA529)	0.073	Nafees et al. (2008)[78]
Arthralgia	30	Assumed (in line with TA529)	0.012	Doyle et al. (2008)[90]
Elevated transaminases	30	Assumed (in line with TA529)	0.000	Doyle et al. (2008)[90]
Hypophosphatemia	30	Assumed (in line with TA529)	0.000	Doyle et al. (2008)[90]
Leukopenia	30	Assumed (in line with TA529)	0.090	Nafees et al. (2008)[78]
Myalgia	30	Assumed (in line with TA529)	0.131	Doyle et al. (2008)[90]
Neutropenia	30	Assumed (in line with TA529)	0.090	Nafees et al. (2008)[78]
Pulmonary embolism	30	Assumed (in line with TA529)	0.012	Doyle et al. (2008)[90]
Thrombocyte	30	Assumed (in line with TA529)	0.000	Nafees et al. (2008)[78]
Weight increased	30	Assumed (in line with TA529)	0.000	Doyle et al. (2008)[90]

Key: AEs, adverse events; TA, technology appraisal.

Table 46: QALY decrements applied in the model

Treatment arm	QALY decrement
Entrectinib	0.001221061
Crizotinib	0.000694993
Pemetrexed plus platinum	0.002126286

Key: QALY, quality-adjusted life year.

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

Pain, mobility functionality and symptom burden as a result of advanced NSCLC were shown to affect the HRQL of a patients.[91] Some of the most common symptoms of lung cancer are cough, shortness of breath (dyspnoea), coughing up phlegm with signs of blood, pain or aching feeling when breathing or coughing, loss of appetite, fatigue, weight loss, and recurrent or persistent chest infection.[92] Using a standard gamble (SG) technique to elicit utilities from a UK population with NSCLC, in Doyle et al (2008)[90] it was shown that pain, cough and dyspnoea resulted in a 0.069, 1.30 and 0.050 decrease in the health state utility values of an individual, respectively.

As described in Section B.3.4.1, pre-progression utility estimates (0.73) from STARTRK-2 are used in the model base case. All treatment arms are considered to have the same utility value. This is considered to be conservative as chemotherapy is associated with side effects which negatively impact patients HRQL and so it is expected that patients on pemetrexed plus platinum would have a lower utility than patients receiving entrectinib and crizotinib. The pre-progression utility value from the STARTRK-2 clinical trial is considered to be the most appropriate as it is the only available utility value in ROS1-positive NSCLC. Utility values from ALK-positive NSCLC patients, previously accepted in TA529 for ROS1-positive NSCLC patients, are tested in a sensitivity analysis.

Given that EQ-5D data were not collected after disease progression in the STARTRK-2 trial, post-progression utilities are assumed to be the same as those used and accepted in TA529. Utilities were sourced from the PROFILE 1007 trial for patients with ALK-positive NSCLC who have progressed and are receiving docetaxel. This is considered to be the most appropriate post-progression value available in the literature considering that patients who progress following treatment with entrectinib, crizotinib or pemetrexed plus platinum would also be treated with docetaxel and these have been previously used and accepted for ROS1-positive patients in TA529.

The approach to capture AE disutility was set out in Section 3.3.4.

In the model, given the long-time horizon, the estimated utilities are adjusted for age over time, based on the Brazier multiplier.[93]

Table 47 details utility values used in the model base case.

Table 47: Summary of utility values used in the cost-effectiveness analysis

Health state	Treatment arm	Utility value: mean (SE)	Reference in submission (section and page number)	Justification
Pre-progression	Entrectinib	0.730 (0.07)	Section B.3.4.1 page 130	Observed in STARTRK-2 for ROS-1 positive patients
	Crizotinib	0.730 (0.07)		As utility data was not collected in PROFILE 1001, it is assumed that patients on crizotinib will have similar utility to patients receiving entrectinib
	Pemetrexed plus platinum	0.730 (0.07)		Conservatively assumed to be the same as entrectinib in absence of ROS1-positive utility data.
Post progression	Entrectinib	0.660 (0.07)	Section B.3.4.5 Page 135	Due to limited observations in STARTRK, estimate from PROFILE 1007 is considered to be the most appropriate, in line with the accepted approach in TA529.
	Crizotinib	0.660 (0.07)	Section B.3.4.5 Page 135	
	Pemetrexed plus platinum	0.660 (0.07)	Section B.3.4.5 Page 135	

Health state	Treatment arm	Utility value: mean (SE)	Reference in submission (section and page number)	Justification
Anaemia	NA	0.073	Section B.3.4.4 page 134	in line with the accepted approach in TA529.
Arthralgia	NA	0.012		in line with the accepted approach in TA529.
Elevated Transaminases	NA	0.000		in line with the accepted approach in TA529.
Hypophosphatemia	NA	0.00		in line with the accepted approach in TA529.
Leukopenia	NA	0.090		in line with the accepted approach in TA529.
Myalgia	NA	0.131		in line with the accepted approach in TA529.
Neutropenia	NA	0.090		in line with the accepted approach in TA529.
Pulmonary embolism	NA	0.012		in line with the accepted approach in TA529.
Thrombocyte	NA	0.000		in line with the accepted approach in TA529.
Weight increased	NA	0.000		in line with the accepted approach in TA529.

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

Costs used within the model reflect the UK NHS perspective and consisted of the following components:

- Drug acquisition costs (including administration costs)
- Monitoring cost
- End-of-life care costs
- Costs associated with the management of adverse events
- ROS1- positive NSCLC testing costs

- Subsequent treatment costs

Resource use and unit costs for the economic model were obtained from a number of sources, including national databases and previous technology appraisals. These are described in more detail below. In the absence of any additional sources of evidence, assumptions were made for cost/resource inputs included in the model where necessary and were validated by clinicians. All model costs were inflated to 2017/2018 when appropriate using inflation indices from the 2018 Personal Social Services Research Unit (PSSRU 2018).[82]

Full details of the systematic review for costs and resource use data are located in Appendix I. No relevant studies were identified in ROS1-positive NSCLC.

Intervention and comparator costs and resource use

Acquisition costs associated with each treatment are presented in Table 48. Prices were taken from the Monthly Index of Medical Specialities (MIMS)[79] for branded products, and the electronic market information tool (eMIT)[80] for the generic products. [79, 80]

Table 48: Unit costs of entrectinib and comparators

Treatment	Unit	Unit cost (list price)	Reference	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Entrectinib	90 x 200mg tablets	[redacted]		3 x 200mg per day (30 days)	[redacted]
	30 x 100mg tablets	[redacted]		6 x 100mg per day (30 days)	[redacted]
Crizotinib	60 x 250mg tablets	£4,689.00	MIMS accessed 2019[79]	2 x 250mg per day (30 days)	£4,689.00
Pemetrexed	100mg vial	£159.67	MIMS accessed 2019[79, 80]	500mg/m^2 once every 3 weeks	£1,418.60
	500mg vial	£795.19			
Cisplatin	10mg (10ml vial)	£1.53	eMIT 2019[80]	75mg/m^2 once every 3 weeks	£11.37
	50mg (50 ml vial)	£4.25			
	100mg (100 ml vial)	£9.26			
Carboplatin	50mg (5 ml vial)	£3.07		AUC 5-6 resulting in 536.49 (based on the Calvert formula)	£15.68
	150mg (15 ml vial)	£6.65			
	450mg (45 ml vial)	£17.03			
	600mg (60 ml vial)	£17.54			

Key: AUC, area under the curve; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; PAS, patients access scheme.

ToT data for entrectinib is taken from the entrectinib integrated trials (ALKA, STARTRK-1/2). The methods used to estimate the ToT data is described in Section B.3.3. The cost of entrectinib per treatment cycle is applied to the proportion of patients treated with entrectinib based on the extrapolated curve. A simple patient access scheme of [redacted] is applied to the acquisition cost of entrectinib.

The methods used to estimate ToT for crizotinib are described in Section B.3.3. The cost of crizotinib per treatment cycle is applied to the proportion of patients treated with crizotinib based on the PFS curve. The list price for crizotinib from MIMS is used in the economic evaluation.

The SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy. In the base case 6 cycles of pemetrexed plus platinum is used in line with the SmPC and TA529. A sensitivity analysis is presented assuming 4 cycles of pemetrexed plus platinum. To align costs and efficacy, where the scenario where MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the chemotherapy arm from the ASCEND-4 trial is used to estimate the pemetrexed plus platinum arm, 4 cycles of pemetrexed plus platinum is assumed followed by 4 cycles of pemetrexed maintenance therapy.

For the pemetrexed plus platinum treatment arm, the distribution of patients across the two platinum regimens is assumed to be as per the final accepted proportion from TA529; cisplatin (54%) or carboplatin (46%). Dosing for pemetrexed and cisplatin were based on the body surface area (BSA) reported in the entrectinib trials (1.78 m^2) in the base case analysis. Carboplatin dosing is based on a target area under the curve (AUC) of 5/6 in line with TA529.

Drug wastage has been assumed in the base case, as this is more likely to reflect the use of therapies in clinical practice. Costs for pemetrexed and cisplatin were calculated using the band dosing method, in line with the NHS England guidelines. The National dose band tables provided by the NHS were used to estimate the optimum combination of vials based on the pre-defined doses in the table.[94] As carboplatin dosing is fixed at 536.49mg, its cost was calculated assuming that clinicians will use the optimum combination of vials to reach the target dose, rounding up to the nearest full vial.

In addition to drug acquisition costs, the cost of administration was considered for entrectinib, crizotinib and chemotherapy (Table 49). Entrectinib and crizotinib are oral therapies and therefore do not require hospital administration. However, given that these are oral chemotherapy we have applied a cost of £140.82 for delivering

oral chemotherapy in the first cycle. For subsequent model cycles, we assume that oral drugs will only incur a dispensing fee cost of £14.59.

For all intravenous chemotherapy regimens, an administration cost of £337.00 was applied in the first cycle for delivering complex chemotherapy at first attendance and an administration cost of £289.00 for delivering subsequent chemotherapy was applied for all subsequent cycles.

Costs associated with treatment administration are summarised in Table 49.

Table 49: Administration costs for entrectinib and comparators

Treatment	Model cycle	Setting	Cost code	Description	Unit cost
Entrectinib (subsequent cycle)	First cycle	Oral	SB11Z	Deliver Exclusively Oral Chemotherapy[81]	£140.82
	Thereafter		NA	Dispensing cost (12 minutes pharmacist time)[82]	£14.59
Crizotinib (subsequent model cycle)	First cycle	Oral	SB11Z	Deliver Exclusively Oral Chemotherapy[81]	£140.82
	Thereafter		NA	Dispensing cost (12 minutes pharmacist time)[82]	£14.59
Pemetrexed plus cisplatin	First cycle	IV	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[81]	£337.00
	Thereafter		SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle[81]	£289.00
Pemetrexed plus carboplatin	First cycle	IV	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance[81]	£337.00
	Thereafter		SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle[81]	£289.00
Key: IV, intravenous; NA, not applicable.					

Health states unit costs and resource use

The details of the health states costs are described in Table 50. Costs are presented for the progression-free health state and the progressed health state. In the model, resource utilisation (monitoring costs) assumptions for the pre-progression and post-progression health states were sourced from TA529. These estimates have also been used in other technology appraisals in NSCLC including TA406[95] and TA296 (replaced by TA422)[96] and TA258[97]. These estimates were viewed as the best available estimates in the literature as they have been subject to review by NICE ERGs and appraisal committees on multiple occasions, including one appraisal assessed specifically for crizotinib in ROS1-positive NSCLC (TA529). In line with TA529, it is assumed that all treatment arms would require the same resource use.

Table 50: Summary of health states and associated costs in the economic model

	Resource required	% patients per month	Frequency per month	Frequency per model cycle (30 days)	Reference	Unit cost	Reference for unit cost
Progression-free	Outpatient visit	100%	0.75	0.74	TA529[38]	£162.05	NHS Reference costs 2017-18, outpatient attendance data-medical oncology (370) [81]
	GP visit	10%	1.00	0.10		£28.00	PSSRU 2018- Clinic consultation lasting 9.22 minutes without qualification costs [82]
	Cancer nurse	20%	1.00	0.20		£89.00	NHS Reference costs 2017-18, Nurse cancer relate adult face to face (N10AF) [81]
	Complete blood count	100%	0.75	0.74		£2.51	NHS Reference costs 2017-18, Direct access: pathology services (DAPS05)[81]
	Biochemistry	100%	0.75	0.74		£1.11	NHS Reference costs 2017-18, Direct access: pathology services (DAPS04) [81]
	CT scan	30%	0.75	0.22		£132.75	NHS Reference costs 2017-18, computerised tomography scan of three areas, with contrast (RD26Z)[81]
	Chest X-ray	30%	0.75	0.22		£31.49	NHS Reference costs 2017-18, direct Access plain film (DAPF)[81]
	Total cost per cycle (30 days)					**£179.19**	

	Resource required	% patients per month	Frequency per month	Frequency per model cycle (30 days)	Reference	Unit cost	Reference for unit cost
Progressed	Outpatient visit	100%	1.00	0.99	TA529[38]	£162.05	NHS Reference costs 2017-18, outpatient attendance data-medical oncology (370) [81]
	GP visit	28%	1.00	0.28		£28.00	PSSRU 2018- Clinic consultation lasting 9.22 minutes without qualification costs [82]
	Cancer nurse	10%	1.00	0.10		£89.00	NHS Reference costs 2017-18, Nurse cancer relate adult face to face (N10AF) [81]
	Complete blood count	100%	1.00	0.99		£2.51	NHS Reference costs 2017-18, Direct access: pathology services (DAPS05)
	Biochemistry	100%	1.00	0.99		£1.11	NHS Reference costs 2017-18, Direct access: pathology services (DAPS04) [81]
	CT scan	5%	0.75	0.04		£132.75	NHS Reference costs 2017-18, computerised tomography scan of three areas, with contrast (RD26Z) [81]
	Chest X-ray	30%	0.75	0.22		£31.49	NHS Reference costs 2017-18, direct Access plain film (DAPF) [81]
	Total cost per cycle (30 days)					**£191.67**	

Key: CT, computed tomography; GP, General practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

It is assumed that all patients are assigned a standard cost for palliative care before death. This is assumed to cover hospital care in the 90 days before dying, based on Georghiou and Bardsley (2014).[98] The costs of terminal care included services such as district nurse, nursing and residential care, hospice care, and Marie Curie nursing. This cost was applied as a one-off cost at the point of death. The total cost is estimated to be £8,756 (see Table 51). This is in line with the previous NICE appraisal in ROS1-positive NSCLC, TA529.[38]

Table 51: Cost of palliative care

Cost	Unit cost	Reference	2017/18 Uplifted cost (PSSRU 2018)[82]
District nurse	£278	Georghiou and Bardsley (2014)[98]	£353
Nursing and residential care	£1,000		£1,285
Hospital care – inpatient	£550		£699
Hospital care – final 3 months of life	£4,500		£5,719
Marie Curie nursing service	£550		£699
Total			**£8,756**
Key: PSSRU, Personal Social Services Research Unit.			

Adverse reaction unit costs and resource use

AEs related costs are applied as a one-off cost in the model. Unit costs were sourced from the latest NHS references costs (2017/2018).[81] In line with TA529, leukopenia, neutropenia and elevated transaminase are assumed to incur no extra costs as they are managed by drug dose reduction. The cost of treating each adverse event is multiplied by the incidence of AEs are reported in Table 53. The total one-off AE cost applied for each arm is reported in Table 52 .

Table 52: AEs one-off costs used in the model

Treatment arm	One-off AEs costs
Entrectinib	£24.18
Crizotinib	£40.80
Pemetrexed plus platinum	£539.75
Key: AEs, adverse events.	

Table 53: AEs costs included in the model

Adverse events	Resource use required	Source	Unit Costs	Source
Anaemia	1.7 hospitalisation days	Assumed (in line with TA529)	£ 293.57	NHS reference costs 2017/18; Iron Deficiency Anaemia with CC Score 0-1 SA04L(day case)[81]
Arthralgia	1 hospitalisation days	Assumed (in line with TA529)	£162.05	NHS reference costs 2017-18 Medical oncology 370 (TA529 assumption) [81]
Elevated transaminases	Managed by dose reduction	Assumed (in line with TA529)		Managed by dose reduction (as per TA529 assumption)[38]
Hypophosphatemia	1.7 hospitalisation days	Assumed (in line with TA529)	£308.88	NHS reference costs 2017/18; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N[81]
Leukopenia	Managed by dose reduction	Assumed (in line with TA529)	£0.00	Managed by dose reduction (as per TA529 assumption)[38]
Myalgia	1 hospitalisation days	Assumed to be same as arthralgia (Elizabeth Wehler et al. 2017)[99]	£162.05	Assumed to be same as arthralgia (Elizabeth Wehler et al. 2017)[99]
Neutropenia	Managed by dose reduction	Assumed (in line with TA529)	£0.00	Managed by dose reduction (as per TA529 assumption)[38]
Pulmonary embolism	5 hospitalisation days	Assumed (in line with the ERG and committee preferred assumption in TA529)	£1,410.51	NHS reference costs 2017/2018 weighted average of Pulmonary Embolus with Interventions-Total HRG activity: DZ09J-Q[81]

Adverse events	Resource use required	Source	Unit Costs	Source
Thrombocyte	2 hospitalisation days	Assumed (in line with TA529)	£277.88	NHS reference costs 2017/18; Thrombocytopenia with CC Score 0-1 SA12K (day case) [81]
Weight increased	No hospitalisation is required	Assumed (in line with TA 529)	£0.00	Assumed to incur no costs (as per TA529 assumption)[38]
Key: AEs, adverse events; CC, cubic centimetre; TA, technology appraisal.				

Miscellaneous unit costs

Testing costs

With the introduction of targeted treatments for ROS1-positive advanced NSCLC, patients are required to undertake the ROS1 testing to confirm their eligibility for targeted therapies. In TA529, upfront ROS1 testing was considered an appropriate approach to apply testing costs. Therefore, in line with the committee's preferred approach, an upfront testing cost was applied to the ROS1 positive targeted therapy arms; entrectinib and crizotinib. 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. This testing approach was also supported by the clinical expert at the validation meeting. [3] Given that the NHS has an existing infrastructure in place to perform and analyse the IHC and FISH tests, acquisition costs of the tests were the only costs considered in the model. It was assumed that the ROS1 incidence rate in non-squamous NSCLC is 1.69%, in line with the assumptions made in TA529.[38]

With the 83% specificity and 100% sensitivity of the IHC ROS1 testing, the rates of false positive and false negative were estimated to be 17% (100%–83%) and 0% (100%–100%), respectively.[38] As FISH for ROS1 testing is the reference test in the diagnostic accuracy, a perfect diagnostics accuracy of FISH ROS1 testing was assumed. In line with TA529, 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 1.69% of patients that are expected to be ROS1-positive where 17% are expected to receive a false negative result. The total ROS1-positive cost testing of £4,285.68 was applied as a one off-cost in the model to both the crizotinib and entrectinib arms. Given that

pemetrexed plus platinum is a general therapy for all advanced NSCLC, it was assumed that patients on that arm will not require ROS1 testing to receive chemotherapy treatments and so they don't incur any testing costs. Table 54 details the derivation of the ROS1 total testing costs.

Table 54: ROS1 testing costs estimation

Test	Cost	Source
IHC	£50	TA529[38]
FISH	£120 IHC: (1.69%+17%) =18.7% Cost of FISH testing £120*18.7% = £22.43	
Total cost of testing	£50+22.43= £72.43	
Total cost per ROS1-positive patient diagnosed	£72.43/1.69% = £4,285.68	
Key: eMIT, electronic market information tool; FISH, fluorescence in situ hybridisation; MIMS, Monthly Index of Medical Specialties; PAS, patients access scheme; IHC, Immunohistochemistry.		

Subsequent treatment costs

In line with the entrectinib clinical trials, upon progression in the model patients move to receive subsequent line of therapy. The majority of patients received chemotherapy such as pemetrexed plus platinum, docetaxel, paclitaxel and gemcitabine. However, a small proportion of patients received immunotherapy such as nivolumab and bevacizumab or TKIs such as crizotinib and erlotinib. The included list of subsequent therapies (Table 55) is broadly reflective of the UK clinical practice and was adjusted to be more reflective of the UK clinical practice and was validated by a clinical expert. [3] It was assumed that patients would not receive the same treatment they received pre-progression again and so it was assumed 0% patients on crizotinib arm would receive crizotinib as a subsequent therapy and 0% patients on pemetrexed arm would receive pemetrexed as a subsequent therapy. In line with the NICE position on therapies in the CDF, crizotinib is not included as a subsequent therapy in the base case comparison.

Due to the lack of comparative data from the entrectinib trials, it was assumed that the comparator arms will have similar proportions of subsequent therapies to the entrectinib arm.

Table 55: Proportion of patients receiving subsequent treatment- Sourced from the entrectinib clinical trial and adjusted to align with UK clinical practice

Subsequent therapy	Entrectinib (base case versus pemetrexed plus platinum)	Entrectinib (key scenario analysis versus crizotinib)	Crizotinib	Pemetrexed plus platinum
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]

Upon disease progression, a one-off cost for subsequent treatment is applied which is informed by the average treatment duration, the required treatment dose and the drug cost for each treatment.

Due to lack of data on serum creatinine and glomerular fibrillation rate (GFR) data needed to estimate the required dose of carboplatin from the entrectinib trial, an AUC of 5-6 was used in the model resulting in a 536.49mg dose. A similar approach used in the pemetrexed platinum arm was used to estimate the drug administration costs for all IV treatments; that is using the NHS reference costs code SB14Z for the first cycle and SB15Z thereafter. As for the oral chemotherapy, we have applied a cost of £140.82 for delivering oral chemotherapy in the first cycle and assumed that patients will only incur a dispensing fee cost of £14.59, thereafter.

Table 56: Subsequent treatment acquisition costs

Treatment	Dose	Frequency	Unit size (mg)	Unit cost	Source
Pemetrexed	500.00mg/m2	Day 1 of 21-day cycle (IV)	100	£159.67	MIMS[79]
			500	£795.19	
Carboplatin	AUC 5–6 IV		50	£3.07	eMIT[80]
			450	£17.03	
			600	£17.54	
			150	£6.65	
Cisplatin	75.00mg/m2		10	£1.53	eMIT77
			50	£4.25	
			100	£9.26	
Nivolumab	3.00mg/Kg	Day 1 of 14-day cycle (IV)	40	£439.00	MIMS[79]
			100	£1,097.00	
			240	£2,633.00	
Crizotinib	500.00mg	Daily (oral)	30 (250mg)	£4,689	MIMS[79]
Docetaxel	75.00mg/m2	Day 1 of 21-day cycle (IV)	20	£5.75	eMIT77
			80	£11.95	
			160	£30.82	
Gemcitabine	1000.00mg/m2	Day 1 and 8 of 21-day cycle (IV)	1,200	£32.21	eMIT77
			1,600	£36.02	
			1,800	£38.82	
			2,000	£42.86	
			2,200	£44.98	
			200	£4.48	
Paclitaxel	200.00mg/m2	Day 1 of 21-day cycle (IV)	100	£9.49	eMIT77
			150	£24.01	
			300	£25.26	
			30	£8.62	
Bevacizumab	11.25mg/Kg	Day 1 of 21-day cycle (IV)	100	£242.66	MIMS[79]
			400	£924.40	
Erlotinib	150.00mg	Daily (oral)	30 (25mg)	£378.33	MIMS[79]
			30 (100mg)	£1324.14	
			30 (150mg)	£1631.53	

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialties.

Chemotherapy treatment duration was assumed to be 3.3 months in line with TA428.[74] Nivolumab and bevacizumab were assumed to have an average dose of 12.6 and 8.9, respectively. This is in line with TA484[73] and Trial E4599.[100] Erlotinib

was assumed to have an average treatment duration of 11 months, based on TA310.[101] As discussed in Section B.3.3, due to the absence of the publicly available ToT data from PROFILE 1001, it was assumed that crizotinib is given until progression resulting in a median PFS of 19.22 months.

The average one-off cost of subsequent therapy was estimated using the proportion of patients across the three arms (as detailed in Table 55) resulting in a one-off total cost of £4,815, £3,541, £8,305 and £4,815 for the entrectinib versus pemetrexed plus platinum, pemetrexed plus platinum arms, crizotinib and entrectinib versus crizotinib, respectively which was applied upon progression.

Table 57: Subsequent therapy costs applied in the model

Subsequent treatment	Dose per administration (mg)	Weeks per administration	Duration of treatment (months)	Acquisition costs per administration /pack	Average Total administration cost	Total one-off cost
Pemetrexed	891.99	3	3.3	£1,418.60	£1,563.88	£8,349.08
Carboplatin	536.49			£15.68		£75.01
Cisplatin	133.80			£11.37		£54.40
Nivolumab	213.23	2	5.8	£2,339.17	£3,689.40	£33,162.92
Crizotinib	500.00	0	19.22	£156.30	£158.98	£91,848
Docetaxel	133.80	3	3.3	£19.99	£1,430.30	£1,525.89
Gemcitabine	1,783.97	1.5	3.3	£36.47	£2,620.10	£2,969.01
Paclitaxel	356.79	3	3.3	£30.04	£1,430.30	£1,573.99
Pemetrexed disodium	891.99	3	8.3	£1,418.60	£1,563.88	£18,587.03
Bevacizumab	799.62	3	6.1	£1,847.93	£2,620.10	£19,066.70
Erlotinib	150.00	0.14	11	£54.38	£162.83	£18,371.39

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

Summary of base case analysis inputs

A summary of key model parameters is provided in Table 58.

Table 58: 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
Model controls			
Time horizon (years)	30	NA	Section B.3.2
Cycle length (days)	30	NA	
Discount rate for costs	3.5%	0% and 5% tested in OWSA, not varied in the PSA.	
Efficacy discount rate	3.5%		
Patients' characteristics			
Mean age	[redacted]	[redacted]	Section B.2.9
Mean body weight	[redacted]	[redacted]	
Mean body height	[redacted]	[redacted]	
Mean body surface area	[redacted]	[redacted]	
Percent female	[redacted]	[redacted]	
Utility inputs			
Utility- PFS health state in ROS1 - Entrectinib	0.73	Beta (0.58-0.86)	Section B.3.4.1
Utility- PFS health state in ROS1 - Crizotinib	0.73	Beta (0.58-0.86)	
Utility-PFS health state in ROS1 - pemetrexed	0.73	Beta (0.58-0.86)	
Utility-PPS health state in ROS1 - Entrectinib	0.66	Beta (0.53-0.78)	Section B.3.4.5
Utility-PPS health state in ROS1 - Crizotinib	0.66	Beta (0.53-0.78)	
Utility-PPS health state in ROS1 - pemetrexed	0.66	Beta (0.53-0.78)	
Disutility			
Associated utility decrement-Anaemia	0.07	Beta (0.06-0.09)	Section B.3.4.5
Associated utility decrement-Arthralgia	0.01	Beta (0.01-0.014)	
Associated utility decrement- Elevated transaminases	0.00	Beta (0.00-0.00)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Associated utility decrement- Hypophosphatemia	0.00	Beta (0.00-0.00)	
Associated utility decrement- Leukopenia	0.09	Beta (0.07-0.11)	
Associated utility decrement-Myalgia	0.13	Beta (0.11-0.16)	
Associated utility decrement- Neutropenia	0.09	Beta (0.07-0.11)	
Associated utility decrement- Pulmonary embolism	0.01	Beta (0.01-0.014)	
Associated utility decrement- Thrombocytopenia	0.00	Beta (0.00-0.00)	
Associated utility decrement- Weight increased	0.00	Beta (0.00-0.00)	
AEs durations			
AE duration (days)- Anaemia	30.00	Normal (24.12-35.88)	Section B.3.4.4
AE duration (days)- Arthralgia	30.00	Normal (24.12-35.88)	
AE duration (days)- Elevated transaminases	30.00	Normal (24.12-35.88)	
AE duration (days)- Hypophosphatemia	30.00	Normal (24.12-35.88)	
AE duration (days)- Leukopenia	30.00	Normal (24.12-35.88)	
AE duration (days)- Myalgia	30.00	Normal (24.12-35.88)	
AE duration (days)- Neutropenia	30.00	Normal (24.12-35.88)	
AE duration (days)- Pulmonary embolism	30.00	Normal (24.12-35.88)	
AE duration (days)- Thrombocytopenia	30.00	Normal (24.12-35.88)	
AE duration (days)- Weight increased	30.00	Normal (24.12-35.88)	
% AEs in the entrectinib arm			
% AE Entrectinib arm- Anaemia	[redacted]	[redacted]	Section B.3.4.4
% AE Entrectinib arm- Arthralgia	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% AE Entrectinib arm-Elevated transaminases	[redacted]	[redacted]	
% AE Entrectinib arm-Hypophosphatemia	[redacted]	[redacted]	
% AE Entrectinib arm-Leukopenia	[redacted]	[redacted]	
% AE Entrectinib arm-Myalgia	[redacted]	[redacted]	
% AE Entrectinib arm-Neutropenia	[redacted]	[redacted]	
% AE Entrectinib arm-Pulmonary embolism	[redacted]	[redacted]	
% AE Entrectinib arm-Thrombocytopenia	[redacted]	[redacted]	
% AE Entrectinib arm-Weight increased	[redacted]	[redacted]	
% AEs in the crizotinib arm			
% AE crizotinib arm-Anaemia	0.00%	Beta (0.00-0.00)	Section B.3.4.4
% AE crizotinib arm-Arthralgia	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Elevated transaminases	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Hypophosphatemia	13.21%	Beta (0.06-0.23)	
% AE crizotinib arm-Leukopenia	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Myalgia	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Neutropenia	9.43%	Beta (0.04-0.19)	
% AE crizotinib arm-Pulmonary embolism	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Thrombocytopenia	0.00%	Beta (0.00-0.00)	
% AE crizotinib arm-Weight increased	0.00%	Beta (0.00-0.00)	
% AEs in the pemetrexed plus platinum			
% AE pemetrexed arm-Anaemia	8.88%	Beta (0.05-0.13)	Section B.3.4.4
% AE pemetrexed arm-Arthralgia	0.00%	Beta (0.00- 0.00)	
% AE pemetrexed arm-Elevated transaminases	2.34%	Beta (0.01-0.05)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% AE pemetrexed arm-Hypophosphatemia	0.00%	Beta (0.00- 0.00)	
% AE pemetrexed arm-Leukopenia	5.33%	Beta (0.02-0.09)	
% AE pemetrexed arm-Myalgia	0.00%	Beta (0.00- 0.00)	
% AE pemetrexed arm-Neutropenia	15.38%	Beta (0.10-0.21)	
% AE pemetrexed arm-Pulmonary embolism	6.51%	Beta (0.03-0.11)	
% AE pemetrexed arm-Thrombocytopenia	6.51%	Beta (0.03-0.11)	
% AE pemetrexed arm-Weight increased	0.00%	Beta (0.00- 0.00)	
Proportion of patients on subsequent therapy upon progression (Base case Proportion sourced from the entrectinib clinical trial adjusted post-clinical validation)			
Entrectinib arm versus pemetrexed plus platinum (base case)			
% Entrectinib-Entrectinib arm	[redacted]	[redacted]	Section B.3.5
% Pemetrexed-Entrectinib arm	[redacted]	[redacted]	
% Carboplatin-Entrectinib arm	[redacted]	[redacted]	
% Cisplatin-Entrectinib arm	[redacted]	[redacted]	
% Nivolumab-Entrectinib arm	[redacted]	[redacted]	
% Crizotinib-Entrectinib arm	[redacted]	[redacted]	
% Docetaxel-Entrectinib arm	[redacted]	[redacted]	
% Gemcitabine-Entrectinib arm	[redacted]	[redacted]	
% Paclitaxel-Entrectinib arm	[redacted]	[redacted]	
% Pemetrexed disodium-Entrectinib arm	[redacted]	[redacted]	
% Bevacizumab-Entrectinib arm	[redacted]	[redacted]	
% Erlotinib-Entrectinib arm	[redacted]	[redacted]	
Entrectinib arm versus crizotinib (key scenario analysis)			
% Entrectinib-Entrectinib arm	0.00%	Beta (0.00-0.00)	Section B.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% Pemetrexed-Entrectinib arm	[redacted]	[redacted]	
% Carboplatin-Entrectinib arm	[redacted]	[redacted]	
% Cisplatin-Entrectinib arm	[redacted]	[redacted]	
% Nivolumab-Entrectinib arm	[redacted]	[redacted]	
% Crizotinib-Entrectinib arm	[redacted]	[redacted]	
% Docetaxel-Entrectinib arm	[redacted]	[redacted]	
% Gemcitabine-Entrectinib arm	[redacted]	[redacted]	
% Paclitaxel-Entrectinib arm	[redacted]	[redacted]	
% Pemetrexed disodium-Entrectinib arm	[redacted]	[redacted]	
% Bevacizumab-Entrectinib arm	[redacted]	[redacted]	
% Erlotinib-Entrectinib arm	[redacted]	[redacted]	
Crizotinib arm			
% Entrectinib-Crizotinib arm	[redacted]	[redacted]	Section B.3.5
% Pemetrexed-Crizotinib arm	[redacted]	[redacted]	
% Carboplatin-Crizotinib arm	[redacted]	[redacted]	
% Cisplatin-Crizotinib arm	[redacted]	[redacted]	
% Nivolumab-Crizotinib arm	[redacted]	[redacted]	
% Crizotinib-Crizotinib arm	[redacted]	[redacted]	
% Docetaxel-Crizotinib arm	[redacted]	[redacted]	
% Gemcitabine-Crizotinib arm	[redacted]	[redacted]	
% Paclitaxel-Crizotinib arm	[redacted]	[redacted]	
% Pemetrexed disodium-Crizotinib arm	[redacted]	[redacted]	
% Bevacizumab-Crizotinib arm	[redacted]	[redacted]	
% Erlotinib-Crizotinib arm	[redacted]	[redacted]	
Pemetrexed plus platinum arm			
% Entrectinib-Pemetrexed plus platinum arm	[redacted]	[redacted]	Section B.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% Pemetrexed-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Carboplatin-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Cisplatin-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Nivolumab-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Crizotinib-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Docetaxel-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Gemcitabine-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Paclitaxel-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Pemetrexed disodium-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Bevacizumab-Pemetrexed plus platinum arm	[redacted]	[redacted]	
% Erlotinib-Pemetrexed plus platinum arm	[redacted]	[redacted]	
Subsequent treatment average number of doses/packs			
Entrectinib average duration	18.23	Gamma (14.83-21.97)	Section B.3.5
Pemetrexed with Carboplatin or cisplatin average duration	4.78	Gamma (3.89-5.76)	
Nivolumab average duration	12.60	Gamma (10.25-15.19)	
Crizotinib average duration	19.5	Gamma (15.87-23.50)	
Docetaxel average duration	4.78	Gamma (3.89-5.76)	
Gemcitabine average duration	9.57	Gamma (7.78-11.53)	
Paclitaxel average duration	4.78	Gamma (3.89-5.76)	
Pemetrexed disodium average duration	12.00	Gamma (9.76-14.46)	
Bevacizumab average duration	8.90	Gamma (7.24-10.73)	
Erlotinib average duration	11.16	Gamma (9.08-13.45)	
Hazard ratio			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PFS HR for Crizo versus pemetrexed	0.45	Log normal (0.35-0.60)	Section B.3.3
PFS HR for Entrec. versus Crizo	[redacted]	[redacted]	
PFS HR for Entrec. versus Crizo IA	[redacted]	[redacted]	
PFS HR for Entrec versus chemo_ASCEND4	[redacted]	[redacted]	
OS HR for Crizo versus pemetrexed	0.35	Log normal (0.08-0.78)	
OS HR for Entrec. versus Crizo	[redacted]	[redacted]	
OS HR for Entrec versus pemetrexed _ASCEND4	[redacted]	[redacted]	
Resource use frequency per cycle			
Frequency per cycle Outpatient visit-PFS	0.74	Beta (0.58-0.87)	Section B.3.5
Frequency per cycle GP visit-PFS	0.10	Beta (0.08-0.12)	
Frequency per cycle Cancer nurse-PFS	0.20	Beta (0.16-0.24)	
Frequency per cycle Complete blood count-PFS	0.74	Beta (0.58-0.87)	
Frequency per cycle Biochemistry -PFS	0.74	Beta (0.58-0.87)	
Frequency per cycle CT scan-PFS	0.22	Beta (0.18-0.27)	
Frequency per cycle Chest X-ray-PFS	0.22	Beta (0.18-0.27)	
Frequency per cycle Outpatient visit-PPS	0.99	Beta (0.04-1.00)	
Frequency per cycle GP visit-PPS	0.28	Beta (0.22-0.33)	
Frequency per cycle Cancer nurse-PPS	0.10	Beta (0.08-0.12)	
Frequency per cycle Complete blood count-PPS	0.99	Beta (0.04-1.00)	
Frequency per cycle Biochemistry -PPS	0.99	Beta (0.04-1.00)	
Frequency per cycle CT scan-PPS	0.04	Beta (0.03-0.04)	
Frequency per cycle Chest X-ray-PPS	0.22	Beta (0.18-0.27)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Proportion receiving cisplatin	0.54	Beta (0.43-0.64)	
Drug costs			
Entrectinib unit cost	[redacted]	[redacted]	Section B.3.5
Entrectinib unit cost	[redacted]	[redacted]	
Crizotinib unit cost	78.15	Normal (62.83-9347)	
Pemetrexed Small composition	159.67	Normal (128.38-190.96)	
Pemetrexed Large composition	795.19	Normal (639.34-951.01)	
Carboplatin Small composition	3.07	Normal (2.47-3.67)	
Carboplatin Large composition	17.03	Normal (13.69-20.37)	
Carboplatin Large composition	17.54	Normal (14.10-20.98)	
Carboplatin Large composition	6.65	Normal (5.35-7.95)	
Cisplatin Small composition	1.53	Normal (1.23-1.83)	
Cisplatin Large composition	4.25	Normal (3.42-5.08)	
Cisplatin 100mg unit cost	9.26	Normal (7.45-11.07)	
Docetaxel 20mg unit cost	5.75	Normal (4.62-6.88)	
Docetaxel 80mg unit cost	11.95	Normal (9.61-14.29)	
Docetaxel 160mg unit cost	30.82	Normal (24.78-38.86)	
Nivolumab 40mg unit cost	439.00	Normal (352.96-525.04)	
Nivolumab 100mg unit cost	1,097.00	Normal (881.99-1,312)	
Nivolumab 240mg unit cost	2,633.00	Normal (2,116.94-3,149.06)	
Gemcitabine 1200mg unit cost	32.21	Normal (25.90-38.52)	
Gemcitabine 1600mg unit cost	36.02	Normal (28.96-43.08)	
Gemcitabine 1800mg unit cost	38.82	Normal (31.21-46.43)	
Gemcitabine 2000mg unit cost	42.86	Normal (34.46-51.26)	
Gemcitabine 2200mg unit cost	44.98	Normal (36.16-53.80)	
Gemcitabine 200mg unit cost	4.48	Normal (3.60-5.36)	
Paclitaxel 100mg unit cost	9.49	Normal (7.63-11.35)	
Paclitaxel 150mg unit cost	24.01	Normal (19.30-28.72)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Paclitaxel 300mg unit cost	25.26	Normal (20.31-30.21)	
Paclitaxel 30mg unit cost	8.62	Normal (6.93-10.31)	
Bevacizumab 100mg unit cost	242.66	Normal (195.10-290.22)	
Bevacizumab 400mg unit cost	924.40	Normal (743.22-1,105.58)	
Erlotinib 750 mg	0.50	Normal (0.41-0.60)	
Erlotinib 3,000 mg	0.44	Normal (0.35-0.53)	
Erlotinib 4,500 mg	0.36	Normal (0.29-0.43)	
Administration costs			
IV administration costs- first cycle	337.00	Normal (270.95-403.05)	Section B.3.5
Oral chemotherapy administration costs	140.82	Normal (113.22-168.42)	
IV administration costs- subsequent cycles	289.00	Normal (232.36-345.64)	
Oral administration costs - dispensing fee costs	14.59	Normal (11.73-17.45)	
ROS1 testing costs			
Cost of IHC	50.00	Normal (40.20-59.80)	Section B.3.5
Proportion of true-positive from IHC	0.017	Beta (0.014-0.02)	
Proportion of false-positive from IHC	0.170	Beta (0.138-0.205)	
Cost of FISH	120.00	Normal (96.48-143.52)	
Incidence of ROS1	0.017	Beta (0.01-0.02)	
Resource use unit costs			
Outpatient visit-cost	162.05	Normal (130.29-193.81)	Section B.3.5
GP visit-cost	28.00	Normal (22.51-33.49)	
Cancer nurse-cost	89.00	Normal (71.56-106.44)	
Complete blood count-cost	2.51	Normal (2.01-3.00)	
Biochemistry -cost	1.11	Normal (0.89-1.33)	
CT scan-cost	132.75	Normal (106.73-158.77)	
Chest X-ray-cost	31.49	Normal (25.31-37.66)	
Adverse events costs			
AEs costs- Anaemia	499.08	Normal (401.26-596.90)	Section B.3.5
AEs costs- Arthralgia	162.05	Normal (130.29-193.81)	
AEs costs- Elevated transaminases	350.15	Normal (281.52-418.78)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AEs costs- Hypophosphatemia	308.88	Normal (248.34-396.41)	
AEs costs- Leukopenia	0.00	Normal (0.00-0.00)	
AEs costs- Myalgia	162.05	Normal (130.29-193.81)	
AEs costs- Neutropenia	0.00	Normal (0.00-0.00)	
AEs costs- Pulmonary embolism	175.40	Normal (141.02-209.78)	
AEs costs- Thrombocytopenia	557.76	Normal (448.44-667.08)	
AEs costs- Weight increased	0.00	Normal (0.00-0.00)	
Terminal care costs			
Terminal care costs	8,755.76	Normal (7,039.66-10,471.85)	Section B.3.5
Curve fit parameters (OS) – Exponential (Entrectinib integrated trials analysis)			
Curve fit parameter OS: Rate	[redacted]	Multinormal distribution	Section B.3.3
Curve fit parameters (PFS) – Exponential (Entrectinib integrated trials analysis)			
Curve fit parameter PFS: Rate	[redacted]	Multinormal distribution	Section B.3.3
Curve fit parameters (ToT) – Exponential (Entrectinib integrated trials analysis)			
Curve fit parameter ToT: Rate	[redacted]	Multinormal distribution	Section B.3.3

Key: ToT, time on treatment, PFS, progression-free survival; OS, overall survival; IHC, Immunohistochemistry ; CT, computerised tomography ; IV, intravenous ; FISH, fluorescence in situ hybridisation; AEs; adverse events; HR, hazard ratio.

Assumptions

A summary of key assumptions is provided in Table 59.

Table 59: Summary of assumptions used in the model

Assumption	Assumption description	Justification
Time Horizon	30 years (lifetime horizon)	The economic model runs for 30 years to reflect the extrapolated life expectancy of the full entrectinib cohort. The impact of varying time horizon on the results is tested in sensitivity analysis.
Carboplatin target dose	AUC 5-6	In line with assumptions made and accepted in TA529
Max number of cycles of pemetrexed chemotherapy	A maximum number of 6 cycles, in line with the NHS clinical practice.	In line with the SmPC, pemetrexed plus platinum are given for a maximum of 6 cycles. This is in line with TA529 and the median ToT from PROFILE 1014.
Cisplatin/carboplatin proportion in combination with pemetrexed chemotherapy	46% of patients receive carboplatin and 54% cisplatin	In line with assumptions made and accepted in TA529
Resource use utilisation	Resource use utilisation is assumed to be the same on all arms	In line with assumptions made and accepted in TA529
ROS-1 testing	The costs of ROS1 testing is applied for the crizotinib and entrectinib arm. Upfront testing approach is used in line with the accepted approach in TA529	In line with committee preferred assumptions in TA529
Entrectinib PFS base case curve	Exponential	The exponential curve was selected for the base case as it had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided a plausible extrapolation
Entrectinib OS base case curve	Exponential	The exponential curve was selected for the base case as it had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided a plausible extrapolation

Assumption	Assumption description	Justification
Entrectinib ToT base case curve	Exponential	The exponential curve was selected for the base case as it had a similar statistical fit to the observed data compared with other curves (based on the AIC, BIC) and provided a plausible extrapolation
Utility values in progression-free	Utilities are assumed to the be the same for all treatment arms	ROS1-positive NSCLC utilities are not available for crizotinib and pemetrexed plus platinum. This is a conservative assumption as it would be expected the chemotherapy would be associated with a lower QoL
Pemetrexed plus platinum efficacy data source	The published HR from PROFILE 1014 was applied to the crizotinib arm.	This would assume that the treatment affect is the same in ROS1 as ALK but doesn't make the assumption that the populations are the same. The used HR has been previously accepted by NICE TA529.
Comparator	Base case: Pemetrexed plus platinum As a key scenario: crizotinib	While recognising the NICE position on the inclusion of cancer drugs fund (CDF) treatments as comparators in the base case, we believe that crizotinib is the most clinically relevant comparison in the treatment of ROS-1 positive patients, aligning with the current clinical practice in NHS England and the March 2019 published NICE guidelines on lung cancer diagnosis and management [NG122]10 for ROS1-positive patients. According to advice we have received from the NICE technical team, and on the basis that we are proactively targeting a CDF recommendation, we have included full results with crizotinib as comparator in scenario analyses. Also, for the abovementioned justification, crizotinib was used to estimate the pemetrexed plus platinum arm; the main comparator in the model base case.
Key: OS, overall survival; PFS, progression-free survival; ToT, time on treatment; NHS, national health services; SmPC, summary of product characteristics.		

B.3.7. Base case results

In the model base case where pemetrexed plus platinum is considered the comparator, discounted model results with a PAS applied to the entrectinib arms are presented in Table 60. The results excluding the PAS are presented in Appendix M. Using a 30-year time horizon, the incremental total LYs gain of entrectinib versus pemetrexed plus platinum-based was [redacted]. The discounted incremental costs of [redacted] and incremental QALYs of [redacted] resulted in an ICER of £15,628 versus pemetrexed plus platinum; This is below the willingness to pay threshold of £50,000.

In the model key scenario where crizotinib is considered as a relevant comparator, discounted model results with a PAS applied to the entrectinib arms and crizotinib at list price are presented in Table 61. Using a 30-year time horizon, the incremental total LYs gain of entrectinib versus crizotinib was [redacted] and incremental QALYs of [redacted]. The discounted incremental costs were [redacted] when including the PAS discount for entrectinib compared to crizotinib at list price.

The results excluding the PAS are presented in Appendix M. At list price, entrectinib is shown to be a cost-effective treatment against both pemetrexed plus platinum and crizotinib; resulting in an ICER of [redacted] and [redacted], respectively.

Table 60: Base case results: entrectinib (with PAS) versus pemetrexed plus platinum (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,930	1.43	1.01				
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,628

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 61: Key scenario results: entrectinib (with PAS) versus crizotinib (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]				
Crizotinib	137,637	3.79	2.63	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. 2,000 iterations were used to ensure convergence. The total costs, LYs and QALYs were recorded for each iteration and averaged.

PSA results for the comparison to pemetrexed plus platinum are presented in Table 62. The results excluding the PAS are presented in Appendix M. The deterministic ICER for entrectinib versus pemetrexed plus platinum (£15,628) is in line with the PSA results of £15,716.

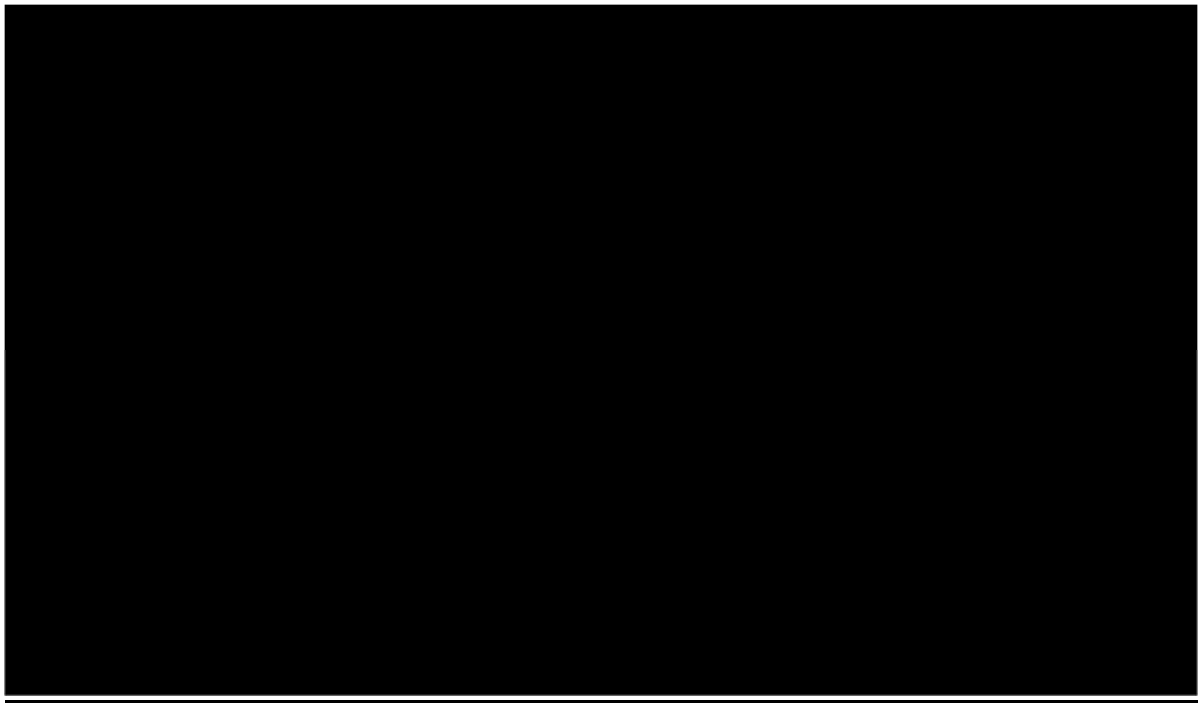
Table 62: Probabilistic sensitivity analysis results: entrectinib (with PAS) versus pemetrexed plus platinum (list price) – base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,629	1.52	1.07				
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,716

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 29 represents the scatter plot of the incremental costs and QALYs from the PSA results based on 2,000 iterations. In 100% of the PSA iteration, the ICER for entrectinib versus pemetrexed plus platinum was below the WTP threshold of £50,000. In addition, as shown in the cost-effectiveness acceptability curve (Figure 30), entrectinib has a 100% probability of being cost-effective versus pemetrexed plus platinum considering the £50,000 WTP threshold.

Figure 29: Cost-effectiveness plane – entrectinib (with PAS) versus pemetrexed plus platinum (list price)- base case



Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 30: CEAC – entrectinib (with PAS) versus pemetrexed plus platinum (list price) – base case

Key: CEAC, cost-effectiveness acceptability curve; PAS, patient access scheme.

Results for the PSA for the key scenario analysis comparison to crizotinib are presented in Table 63. In both the PSA and deterministic results entrectinib dominated crizotinib, when considering the PAS discount for entrectinib and crizotinib at list price, as it was positioned in the south east quadrant of the cost-effectiveness plane. The results excluding the PAS are presented in Appendix M.

Table 63: Probabilistic sensitivity analysis results: entrectinib (with PAS) versus crizotinib (at list price)- key scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]				
Crizotinib	£138,957	3.93	2.73	[redacted]	[redacted]	[redacted]	Entrectinib is dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 31 represents the scatter plot of the incremental costs and QALYs from the PSA results based on 2,000 iterations. When considering the PAS discount for

entrectinib and crizotinib at list price, in 100% of the PSA iterations, the ICER for entrectinib versus crizotinib was placed in the south east quadrant of the cost-effectiveness plane; resulting in crizotinib being always cost-effective. In addition, as shown in the cost-effectiveness acceptability curve (Figure 32), entrectinib was shown to be always cost-effective versus crizotinib, irrespective of the WTP threshold.

Figure 31: Cost-effectiveness plane – entrectinib (with PAS) applied versus crizotinib (at list price) - key scenario

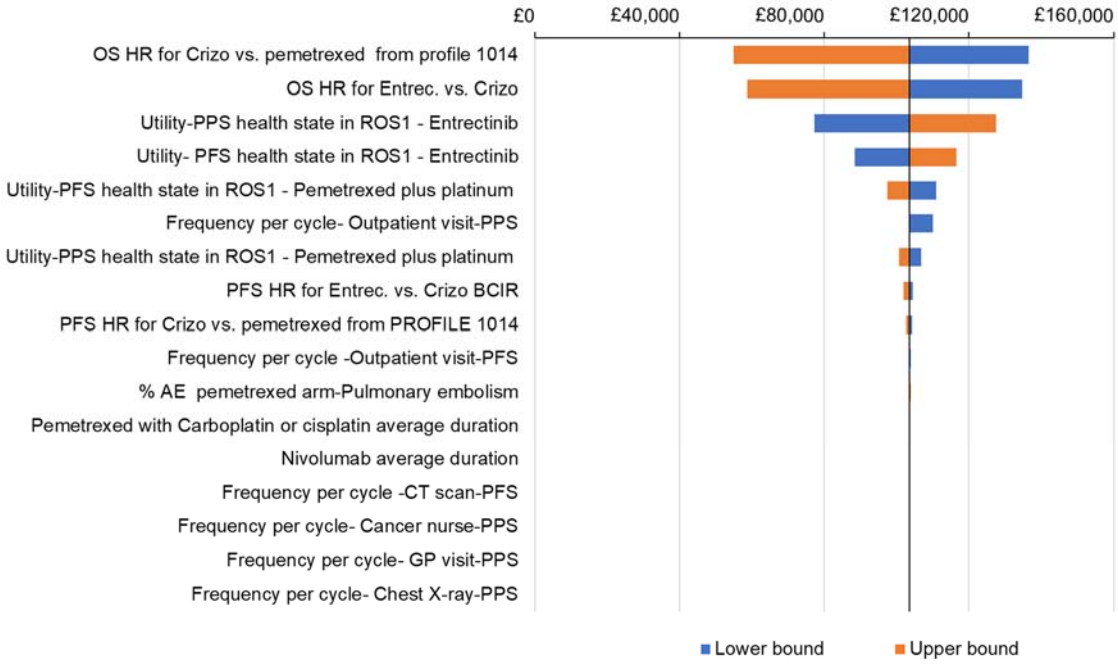
Figure 32: CEAC – entrectinib (with PAS) versus crizotinib (at list price)- key scenario

Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to investigate key drivers of the cost-effectiveness model.

The tornado diagram for entrectinib versus pemetrexed plus platinum is presented in Figure 33. The OWSA used net monetary benefit. This showed that both OS HR for crizotinib versus pemetrexed plus platinum and entrectinib versus crizotinib had the great impact on the cost-effectiveness results. It is unsurprising that the OS HR for crizotinib versus entrectinib was most influential given that pemetrexed plus platinum arm is derived using the estimated crizotinib arm in the model. These parameters drive the incremental difference in OS between the entrectinib and pemetrexed plus platinum arms, and therefore affects the overall QALYs and costs attributed to each treatment arm.

Figure 33: Tornado diagram (NMB): entrectinib (with PAS) versus pemetrexed plus platinum-based (list price)– base case

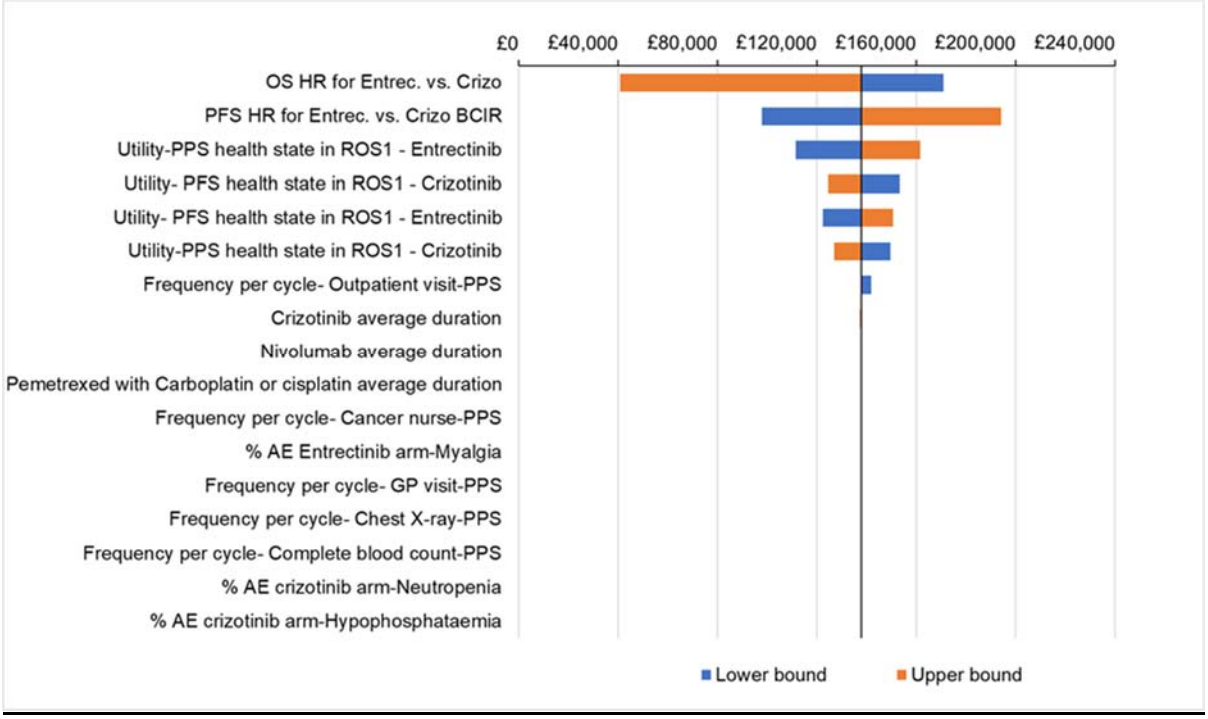


Key: AE, adverse event; Crizo, crizotinib; CT, computerised tomography; GP, general practitioner; HR, hazard ratio; NMB; net monetary benefit; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival.

The tornado diagram for entrectinib versus crizotinib is presented in Figure 34. This showed that the OS and PFS HR for entrectinib versus crizotinib followed by the PFS and PPS utility for the entrectinib are the parameters with the greatest impact on the cost-effectiveness. It is unsurprising that the OS HR had the great impact

given the large CI as a result of small patient number and immaturity of the OS data used in the MAIC.

Figure 34: Tornado diagram (NMB): entrectinib (with PAS) applied versus crizotinib (list price)– key scenario



Key: AE, adverse event; CT, computerised tomography; GP, general practitioner; HR, hazard ratio; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival.

Scenario analysis

The list of scenarios explored in the model are listed in Table 64 and results include a PAS for entrectinib presented in

Table 65 and Table 66 for the comparison the pemetrexed plus platinum and crizotinib, respectively. Resulting excluding the PAS are reported in Appendix M.

All scenarios presented for entrectinib compared to pemetrexed plus platinum and compared to crizotinib resulted in ICERs that fell below the £50,000 willingness to pay threshold.

Table 64: Scenario analysis results- entrectinib (with PAS) versus pemetrexed plus platinum (list price) – base case

No.	Parameters	Scenario	Base case
1	Time Horizon	5-year time horizon	30 years
2		10-year time horizon	
3		20- year time horizon	
4	OS entrectinib curve	Weibull	Exponential
5		Log-logistic	
6	PFS entrectinib curve	Weibull	Exponential
7		Log-logistic	
8	ToT entrectinib curve	Gompertz	Exponential
9		Weibull	
10	Pemetrexed plus platinum based-therapy efficacy input (PFS and OS)	MAIC ASCEND-4 (versus entrectinib) with maximum of 4 cycles followed by 4 cycles of maintenance therapy	PROFILE 1014 HR crizotinib versus pemetrexed
11	Pemetrexed plus platinum based-therapy efficacy input (PFS and OS)	Based on the crizotinib arm estimated from PROFILE 1001	Based on the crizotinib arm estimated from MAIC entrectinib versus crizotinib
12	Pemetrexed plus platinum based-therapy PFS	Pemetrexed arm estimated by applying a HR on the estimated crizotinib arm using resulting HR from MAIC entrectinib versus crizotinib using PFS IA	Pemetrexed arm estimated by applying a HR on the estimated crizotinib arm using resulting HR from MAIC entrectinib versus crizotinib using PFS BICR
13	PFS and OS treatment effect for the entrectinib arm	No treatment effect for PFS after 24 months for the entrectinib arm	Treatment effect is maintained
14		No treatment effect for OS after 24 months for the entrectinib arm	
15		No treatment effect for PFS and OS after 24 months for the entrectinib arm	
16	Discount rate – costs and QALYS	0%	3.5%
17		5%	
18	Proportion of patients receiving carboplatin	25% of patients receiving carboplatin	46% of patients received carboplatin
19	Subsequent therapy treatment cost choice	Using unadjusted entrectinib trial data	Using adjusted entrectinib trial

20	Pemetrexed plus platinum number of cycles	4 cycles	6 cycles

Key: Crizo, crizotinib; entrec, entrectinib; HR, hazard ratio; IA, independent assessor; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Table 65: Scenario analysis results- entrectinib (with PAS) versus pemetrexed plus platinum (list price)

No.	Scenario	ICER versus pemetrexed (£/QALY)
1	5-year time horizon	£25,977
2	10-year time horizon	£18,612
3	20- year time horizon	£16,004
4	OS-Weibull	£13,423
5	OS-Log-logistic	£11,394
6	PFS-Weibull	£15,663
7	PFS- Log-logistic	£15,141
8	ToT- Gompertz	£14,350
9	ToT- Weibull	£16,815
10	MAIC ASCEND-4 (versus entrectinib) with maximum of 4 cycles followed by 4 cycles of maintenance therapy applied to patients who progressed on pemetrexed with cisplatin	£22,339
11	Pemetrexed plus platinum arm estimated by applying a HR on the crizotinib arm that is estimated from PROFILE 1001	£17,041
12	Pemetrexed plus platinum-based therapy arm estimated by applying a HR on the estimated crizotinib arm using resulting HR from MAIC entrectinib versus crizotinib using PFS IA	£15,776
13	No PFS treatment effect post 24 months for the entrectinib arm	£15,903
14	No OS treatment effect post 24 months for the entrectinib arm	£36,873
15	No PFS and OS treatment post 24 months for the entrectinib arm	£37,724
16	0% discount rate-costs/QALYs	£13,895

No.	Scenario	ICER versus pemetrexed (£/QALY)
17	5% discount rate-costs/QALYs	£16,346
18	25% of patients receiving carboplatin	£15,629
19	Using unadjusted entrectinib trial data	£16,048
20	4 cycles of pemetrexed plus platinum	£16,862
Key: OS, overall survival; PFS, progression-free survival; ToT, time on treatment; MAIC, matching adjusted indirect comparison; QALY, quality adjusted life year		

Table 66: Scenario analysis results- entrectinib (with PAS) versus crizotinib (list price) – key scenario analysis

No.	Parameters	Scenario	Base case
1	Time Horizon	5-year time horizon	30 years
2		10-year time horizon	
3		20- year time horizon	
4	OS entrectinib curve	Weibull	Exponential
5		Log-logistic	
6	PFS entrectinib curve	Weibull	Exponential
7		Log-logistic	
8	ToT entrectinib curve	Gompertz	Exponential
9		Weibull	
10	Crizotinib PFS/OS	Naïve comparison to PROFILE 1001 (using exponential curves for both PFS and OS)	MAIC versus entrectinib with PFS BICR
11		MAIC versus entrectinib with IA PFS	
12	PFS and OS treatment effect	No treatment effect for PFS after 24 months	Treatment effect is maintained
13		No treatment effect for OS after 24 months	
14		No treatment effect for PFS and OS after 24 months	
15	Discount rate – costs and QALYS	0%	3.5%
16		5%	
Key: Crizo, crizotinib; entrec, entrectinib; HR, hazard ratio; IA, independent assessor; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.			

Table 67: Scenario analysis results for comparison to crizotinib – PAS applied for entrectinib, list price used for crizotinib

No.	Scenario	ICER versus crizotinib (£/QALY)
1	5-year time horizon	Entrectinib is dominant
2	10-year time horizon	Entrectinib is dominant
3	20- year time horizon	Entrectinib is dominant
4	OS-Weibull	Entrectinib is dominant
5	OS-Log-logistic	Entrectinib is dominant
6	PFS-Weibull	Entrectinib is dominant
7	PFS- Log-logistic	Entrectinib is dominant
8	ToT- Gompertz	Entrectinib is dominant
9	ToT- Weibull	Entrectinib is dominant
10	Crizotinib OS/PFS efficacy from PROFILE 1001 (exponential curve for both PFS and OS)	Entrectinib is dominant
11	Crizotinib PFS from MAIC entrectinib versus Crizo using PFS IA	Entrectinib is dominant
12	No PFS treatment effect post 24 months	Entrectinib is dominant
13	No OS treatment effect post 24 months	Entrectinib is dominant
14	No PFS and OS treatment effect post 24 months	Entrectinib is dominant
15	0% discount rate- costs and QALYs	Entrectinib is dominant
16	5% discount rate- costs and QALYS	Entrectinib is dominant

Summary of sensitivity analyses results

Base case

- The ICERs for entrectinib versus pemetrexed plus platinum is well below the WTP threshold of £50,000; entrectinib was cost-effective in 100% of the PSA iterations
- The key drivers of the model were similar to the ones observed in TA529; that is the OS and PFS HR used to estimate the pemetrexed plus platinum treatment arm
- The ICER for entrectinib versus pemetrexed plus platinum remained below the WTP threshold of £50,000 for all scenarios, with most significant increase in the ICER being related to assumption around treatment effect, the choice of data used to estimate the OS and PFS where the MAIC of entrectinib and ASCEND-4 trial is used as well as when a five years-time horizon is employed

Key Scenario analysis

- When considering a [redacted] for entrectinib versus crizotinib at list price, entrectinib was placed in the south-east quadrant of the cost-effectiveness plane thereby offering a more effective treatment with cheaper costs resulting in entrectinib being always cost- effective against crizotinib; entrectinib was dominant in 100% of the PSA iterations
- The key drivers of the model were the OS and PFS HR used to estimate the crizotinib arm, with the most significant increase in the ICER being related to the OS HR from the MAIC of entrectinib versus crizotinib because of the large confidence interval; a result of the low number of events due to the immaturity of the data.
- For all scenarios entrectinib maintained its position in the south-east quadrant of the cost-effectiveness plane, with most significant increase in the ICER being related to assumptions around treatment effect, the choice of curves for the OS and PFS for the entrectinib arm (Weibull and log-logistic), using the naïve comparison to estimate the crizotinib OS and PFS curves and when a five years-time horizon is employed

B.3.9. Subgroup analysis

No subgroup analyses are presented as part of this submission.

B.3.10. Validation

Validation of cost-effectiveness analysis

Outcomes from the relevant clinical trials and TA529 are presented alongside the predicted PFS and OS from the model in Appendix J.

The model slightly under predicts entrectinib PFS compared to the median PFS reported in the integrated ALKA and STARTRK-1/2 trials ([redacted]). This is due to the poor fit to the data as a result of the small patient numbers in the clinical trials. The median PFS for crizotinib in the model is aligned with that reported in the PROFILE 1001 (19.7 months versus 19.2 months).[102] The model median OS for crizotinib in the model is lower than the median OS reported at a recent conference (51.4 months). This data was published after the ITC had been conducted and so the MAIC used data which was very immature (median OS not reached for either crizotinib or entrectinib).

The median PFS for pemetrexed plus platinum in the model is aligned with that reported in PROFILE 1014 (7.89 months versus 7.0 months).[65] However, the median OS for pemetrexed plus platinum in the model is lower than reported in PROFILE 1014 (12.2 months versus 19.2 months).[65] This result was expected given that the pemetrexed plus platinum curve is estimated by applying the published HR of crizotinib versus pemetrexed derived using the new data cut-off date of June 2018, where the reported OS is considered to be overestimating overall survival.

Quality control

The model was quality-assured by an external vendor. In these processes, an economist not involved in the model's construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and the assumptions were questioned.

Clinical experts' validation

Validation of the model assumptions and outcomes were conducted with one clinical expert, practicing in the UK. The clinical expert confirmed that the patient demographics from the integrated ALKA and STARTRK-1/2 analysis is representative of the UK population. [3]

The extrapolated OS, PFS and ToT curves based on the integrated analysis conducted across the three entrectinib studies (ALKA, STARTRK-1 and STARTRK-2) for ROS-1 positive patients and the estimated outcomes for the pemetrexed plus platinum and crizotinib arms were validated by a clinical expert at a validation meeting held in May 2019.[3]

Although the clinical expert agreed that the selected curve results in reasonable long-term extrapolations for the entrectinib OS and PFS, predicted survival outcomes were estimated to be better than may be expected in clinical practice.

Similarly, the clinical expert agreed that the estimated OS and PFS for crizotinib using the HR from the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the crizotinib arm from PROFILE 1001 resulted in reasonable OS and PFS extrapolations for the crizotinib arm. However, it was highlighted that the extrapolated long-term survival outcomes from PROFILE 1001 are much better than is actually seen in clinical practice.

The estimated PFS and OS outcomes for pemetrexed plus platinum was validated by a clinical expert who agreed that the estimated curve using the HR from the MAIC between the integrated analysis of efficacy conducted across the three entrectinib studies and the chemotherapy arm from the ASCEND-4 trial resulted in an overly optimistic proportion of patients alive at 5 years (23.8%) than would be expected in clinical practice. As a result, the curve estimated using the published HR from PROFILE 1014 applied on the estimated crizotinib arm was deemed to be more reflective of what is seen in clinical practice.

B.3.11. Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation comparing entrectinib with crizotinib and pemetrexed plus platinum in patients with ROS1- positive NSCLC

Relevance of the economic evaluation to all patients who could potentially use the technology as identified in the decision problem

This evaluation considers all patients identified in the decision problem.

Generalisability of the analysis

Clinical expert opinion confirmed that the data from ALKA and STARTRK-1/2 is aligned with what they would expect to see in UK clinical practice and thus it can be concluded that the data is generalisable to the UK population. [3]

The model was developed using the NHS Reference costs and costs from previous technology appraisals presented to NICE as a source of cost inputs. These cost inputs are considered most appropriate to model the cost-effectiveness of entrectinib in the UK population, as they have been previously validated by UK clinicians.

In summary, all steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of entrectinib reflective of UK clinical practice.

Strength of the economic evaluation

The economic analysis optimises the use of the limited available data in this patient population, while fully accounting for the clinically and economically relevant parameters in the decision problem.

Model structure and assumptions were based mostly on the accepted approaches presented in TA529. Key model assumptions and uncertainties were extensively explored through sensitivity analyses. In the majority of alternative scenarios presented, entrectinib remains cost-effective compared with crizotinib and pemetrexed plus cisplatin/carboplatin at a willingness to pay threshold of £50,000 per QALY gained.

Limitations of the economic evaluations

The key limitation of the analysis is the small patient numbers in the entrectinib ALKA and STARTRK-1/2 clinical trials. Another key limitation is the lack of direct comparative data in ROS1-positive NSCLC, as such indirect comparisons were required by conducting MAIC versus comparators. There is no evidence available for pemetrexed plus platinum in ROS1-positive NSCLC patients and so comparison to ALK-positive NSCLC patients was made.

Further to this, the immature data, small number of patients and associated events in the ALKA and STARTRK-1/2 clinical trials (even when all available data was integrated) lead to extrapolations of PFS and OS that did not exhibit a good fit to the observed data and that may not be clinically plausible.

Further analysis

Longer-term, comparative data in a larger number of patients with ROS1-positive NSCLC would improve the robustness of the economic evaluation presented here; however, it is recognised that it is unlikely that future comparative analyses are unlikely given ethical constraints.

[redacted]

Conclusion

Entrectinib is proven to be an effective treatment for patients with ROS1- positive NSCLC with a good safety profile. The cost-effectiveness analyses have shown improved outcomes compared with pemetrexed plus platinum and crizotinib as presented in the key model scenario.

The base case results in the economic model, showed that versus pemetrexed, entrectinib is a cost-effective treatment at a WTP threshold of £50,000 with an ICER of £15,628. Entrectinib was demonstrated to be cost-effective against crizotinib irrespective of the WTP threshold; that is offering a cheaper treatment with better survival outcome, when considering the PAS discount for entrectinib and the list price for crizotinib.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Supporting information for Section B.2

Appendix M: Model results with entrectinib list price

1. **Please confirm whether your base case has been updated from the original submission**

We would like to confirm that the original submission will remain the base case analysis. We acknowledge that the ERG's preferred efficacy set (STARTRK-2 only and no restriction on follow-up) is a larger dataset (N=78) from a single Phase II study compared to the primary efficacy set (N=53), and therefore could appear to be a more robust dataset than the smaller dataset across Phase I/II studies. We appreciate that some differences in outcomes across cohorts were observed, however no differences appear to be due to the different follow-up criteria used and the over-all results were consistent with the findings from our original submission.

We believe that the primary efficacy set is more representative, as it is an integrated analysis of efficacy conducted across three studies and therefore combines ROS1+ NSCLC patients from ALKA, STARTRK-1 and STARTRK-2. Restricting to a single study excludes information from the additional studies in a rare disease setting. Additionally, due to the rare disease setting for ROS1+ NSCLC, both the FDA and the EMA agreed with the methodology to pool safety and efficacy data from the clinical studies.

Furthermore, the restriction on follow-up of ≥12 months was advised by the FDA in order to ensure an adequate assessment of durability of response. The exploratory analyses submitted demonstrated that the removal of the follow-up criteria had little impact on PFS and OS, presumably due to the shorter follow up time and the significant censoring in the patient group added to the analysis.

The results of the multiple analyses using the ERG preferred efficacy set were mainly consistent with the results from the primary analysis, demonstrating robustness of the data of the primary efficacy set. The economic outcomes also remained consistent, demonstrating entrectinib to be a highly cost-effective treatment in all scenarios.

Lastly, the primary efficacy set was pre-specified in the protocol in agreement with regulators, whereas the ERG's preferred efficacy set is a post-hoc analysis and will remain exploratory.

2. **Please provide results tables for OS and PFS for the MAICs requested in Questions A6 and A7. The tables should include sample size, number of events, median time to event with 95% CI and the hazard ratio with 95% CI for entrectinib before and after re-weighting, and the comparator.**

The bootstrapping method was used to calculate the reweighted entrectinib hazard ratio 95% CI. For the 95% CI of the median time to event, bootstrapping was not performed given that is it frequently non-estimable.

Table 1: Comparison of entrectinib versus PROFILE 1001 crizotinib – Overall Survival

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib		53	27	51.5 (30.37, NE)	
Key: CI, confidence interval, NE, not estimable; MAIC, matching adjusted indirect comparison					

Table 2: Comparison of entrectinib versus PROFILE 1001 crizotinib – Progression-Free Survival by BICR

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib		53	36	19.33 (15.27, 40.37)	
Key: CI, confidence interval, NE, not estimable; MAIC, matching adjusted indirect comparison					

Table 3: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – Overall survival

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed + Platinum with Pemetrexed Maintenance		187	59	26.26 (22.84, NE)	
Key: CI, confidence interval, MAIC, matching-adjusted indirect comparison; NE, not estimable					

Table 4: Comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum with pemetrexed maintenance – Progression-free survival by BICR

Intervention	Comparator	Sample Size	Number of events	Median time to event, Months (95% CI)	Hazard Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed + Platinum with Pemetrexed Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed + Platinum with Pemetrexed Maintenance		187	117	7.99 (5.7, 11.13)	
Key: CI, confidence interval, MAIC, matching-adjusted indirect comparison; NE, not estimable					

3. **Please provide a description of the rationale used to select the distributions used to fit the new OS, PFS and TTD curves to the ERG's preferred data.**

Similar to the original submission where the primary efficacy set is used, treatment efficacy beyond the trial follow-up period for the ERG's preferred efficacy data set was

derived by fitting parametric survival curves to the OS, PFS and TTD KM data. Survival curve fitting was conducted in line with the NICE DSU TSD 14. All standard parametric models were considered and compared. These included; exponential, Weibull, log-normal, log-logistic, Gompertz and gamma. The fit of the alternative models was assessed by:

- Comparing both the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC), where the model with the lowest AIC/BIC indicates the best statistically fitting curve.
- Performing a visual inspection of the fitted curves.

OS extrapolation:

The AIC/BIC statistics for the entrectinib OS curves are reported in Figure 1. The OS curve fits, alongside the KM curves are presented in

Table *5*.

According to the AIC/BIC statistics, the exponential curve was deemed the best fitting curve with a good visual fit to the KM data. Also, it provides the most conservative long-term survival estimates (11.2% of patients alive at 10 years). Using the primary efficacy set, the exponential curve was also deemed the most appropriate curve for the base case, providing the most clinically plausible OS estimate for entrectinib.

The selection of the exponential curve is in line with the chosen and accepted OS curve for the extrapolation of crizotinib overall survival in ROS1 NSCLC patients as part of TA529.

Figure 1: Visual fit of the OS parametric functions to the entrectinib ROS1 ERG preferred efficacy data set

Table 5: AIC and BIC for entrectinib OS

Model	AIC	BIC
Exponential	192.00	194.30
Weibull	192.70	197.40
Log-normal	192.90	197.60
Gamma	194.60	201.70
Log-logistic	192.80	197.50
Gompertz	193.50	198.30
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.		

PFS extrapolation:

The AIC/BIC statistics for the entrectinib PFS curves using the ERG preferred efficacy data set are reported in Table 6 . The PFS curve fits, alongside the KM curves are presented in Figure 2.

According to the AIC/BIC statistics, the exponential curve was deemed the best fitting curve with a good visual fit to the KM data. Also, it provides the most conservative long-term survival estimates (4.7% of patients in the progression-free at 5 years). Using the primary efficacy set, the exponential curve was also deemed the most appropriate curve for the base case, providing the most clinically plausible PFS estimate for entrectinib (9.9% of patients in the progression-free state at 5 years).

The selection of the exponential curve is in line with the chosen and accepted PFS curve for the extrapolation of crizotinib progression-free survival in ROS1 NSCLC patients as part of TA529.

Figure 2: Visual fit of the PFS parametric functions to the entrectinib ROS1 ERG preferred efficacy data set

Key: KM, Kaplan–Meier; OS, overall survival.

Table 6: AIC and BIC for entrectinib PFS

Model	AIC	BIC
Exponential	335.00	337.40
Weibull	337.00	341.70
Log-normal	339.00	343.70
Gamma	338.90	346.00
Log-logistic	337.60	342.30
Gompertz	337.00	341.70
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.		

TOT extrapolation:

The AIC/BIC statistics for the entrectinib ToT curves are show in Table 7. The ToT curve fits, alongside the KM curves are presented in Figure 3.

According to the AIC/BIC statistics, the exponential curve was deemed the best fitting curve with a good visual fit to the KM data. Also, it provides the most appropriate predicted median ToT of 15.77 months. This is close to the predicted median ToT of 17.74 months using an exponential curve for primary efficacy data set which was considered a reasonable estimate by the Clinical expert falling within the range of the predicted drug's clinical use within the NHS clinical setting.

Figure 3: Visual fit of the ToT parametric functions to the entrectinib ROS1 ERG preferred efficacy data set

Key: KM, Kaplan–Meier; OS, overall survival.

Table 7: AIC and BIC for entrectinib ToT

Model	AIC	BIC
Exponential	350.40	352.80
Weibull	351.20	355.90
Log-normal	354.40	359.10
Gamma	352.30	359.40
Log-logistic	352.90	357.60
Gompertz	352.30	357.00
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Clarification questions

July 2019

File name	Version	Contains confidential information	Date
ID1541 entrectinib ERG clarification letter for company [ACIC]	**2.0**	**Yes**	**17th July 2019**

Cover letter

Please find the completed set of responses to clarification questions in this document, and we thank the ERG and NICE for allowing us the extra time needed to provide these to the detail required.

As you will see when reviewing the responses, there are changes to the clinical outcomes from the entrectinib integrated analyses when the ERG's preferred efficacy set are analysed. Exploration into potential drivers of this difference suggest that this is not due to differences in follow-up times rather than the selected cohort, and these analyses are provided in Appendix A for interest.

Irrespective of whether the primary efficacy set previously provided or the ERG's preferred efficacy set are used, entrectinib is shown to be a highly cost-effective treatment at a WTP threshold of £50,000 for end-of-life treatments and at the standard WTP threshold of £20,000-£30,000.

These further analyses therefore primarily represent the acknowledged uncertainty in the current evidence base for entrectinib but confirm the plausible potential for it to satisfy the criteria for routine commissioning, and thus its suitability for reimbursement through the CDF while further data collection is ongoing.

Summary of response status

A1	Provided 10 July
A2	Provided 10 July
A3	Provided 17 July
A4	Provided 17 July
A5	Provided 17 July
A6	Provided 17 July
A7	Provided 17 July
A8	Provided 10 July
A9	Provided 10 July
A10	Provided 17 July
A11	Provided 10 July
A12	Provided 10 July
B1	Provided 17 July

B2	Provided 10 July
B3	Provided 17 July
B4	Provided 10 July
B5	Provided 10 July
B6	Provided 10 July
B7	Provided 10 July
B8	Provided 10 July
B9	Provided 10 July
B10	Provided 10 July
B11	Provided 10 July
B12	Provided 17 July
B13	Provided 10 July
B14	Provided 10 July
B15	Provided 10 July
B16	Provided 10 July
B17	Provided 10 July
B18	Provided 10 July
B19	Provided 10 July
B20	Provided 10 July
B21	Provided 17 July
B22	Provided 17 July
B23	Provided 17 July
B24	Provided 17 July
B25	Provided 17 July
B26	Provided 17 July
B27	Provided 17 July

Section A: Clarification on effectiveness data

Entrectinib integrated analysis

A1. Priority: Please explain why the primary efficacy set which forms the basis for the matching adjusted indirect comparison (MAIC) is limited to ROS1+ non-small-cell lung cancer (NSCLC) patients with ≥ 12 months' follow-up from the time of first response, which excludes around half of the ROS1+ NSCLC efficacy population across ALKA, STARTRK-1 and STARTRK-2. Please also clarify:

The primary efficacy set included criteria on ≥12 months follow-up based on feedback provided by the FDA in July 2017. The FDA recommended at least 12 months of efficacy follow-up to ensure an adequate assessment of durability of response in a relatively mature and stable dataset. It was also mentioned during EU Scientific Advice, but there was no formal feedback on this at EU level.

a) **Whether all patients included in the primary efficacy set had ROS1+ NSCLC and received entrectinib 600 mg;**

Please see Table 2 for details of entrectinib dosing. Most patients included in the primary efficacy set received entrectinib 600mg including all patients from STARTRK-2 and [redacted] of the [redacted] patients in STARTRK-1. [redacted] in STARTRK-1 was treated with 600-800 mg/day dependent on their body surface area (BSA) but the exact dosing cannot be confirmed. Patients in ALKA were treated according to various dosing schedules reported in the company submission Appendix Table 4 - none of these schedules aligned to a continuous daily dosing regimen of 600mg/day.

b) **whether patients who had not responded to entrectinib were included in the primary analysis set and, if they were, whether there were any minimum follow-up restrictions;**

Patients who had not responded to entrectinib were included in the primary analysis set. All patients with ROS-1+ NSCLC who were ROS1-inhibitor naïve and had measurable disease at baseline and were enrolled prior to 30 April 2017 (and thus

had more than 12 months follow-up at the clinical cut-off date) were included. Please see Table 1 for further clarity.

c) **whether the 12-month follow-up for responders was irrespective of patient status during follow-up (e.g. disease progression, discontinuation of entrectinib, death).**

The 12-month follow-up for responders was irrespective of patient status during follow-up. The only restriction placed on the follow-up of responders was the enrolment date (30th April 2017).

A2. Priority: The ERG has reviewed the clinical study reports (CSRs) provided alongside Figure 2 (Document B) and Figure 5 (Appendix D.2) and has been unable to verify the number of patients included in the primary efficacy set from ALKA and STARTRK-1, and how many received entrectinib 600 mg.* Please provide a more detailed CONSORT diagram to allow the ERG to verify the population included for the primary efficacy set used in the submission against each study CSR, including:

a) **How many of the [redacted] patients with ROS1+ NSCLC are from each study;**

b) **How many of the [redacted] patients in the ROS1+ NSCLC efficacy population are from each study;**

c) **Reasons for exclusion broken down by study for the [redacted] enrolled patients not included in the ROS1+ NSCLC efficacy population;**

d) **Reasons for exclusion broken down by study for the [redacted] patients in the ROS1+ NSCLC efficacy population who were not included in the primary efficacy set;**

e) **The number of patients included in the primary efficacy set who received entrectinib 600 mg.**

***For example, Figure 2 in the CSR for ALKA indicates that [redacted] patients (irrespective of diagnosis) received entrectinib 600 mg in Schedule B, but does not indicate how many patients in any dose group had ROS1+ NSCLC. It is unclear from the submission whether the [redacted] patients included in the integrated**

analysis (primary efficacy set) from ALKA were part of the [redacted] who received 600 mg in Schedule B or if they were part of other dosing schedules. For STARTRK-1, Table 10 of the CSR indicates that [redacted] of the [redacted] patients in the 600 mg QD F2A group had ROS1+ NSCLC, but it is unclear whether the [redacted] patients included in the integrated analysis were all from this group and, if they were, why [redacted] patients were not included in the primary efficacy set.

Please see Table 1 for a more detailed breakdown of the CONSORT diagram, clearly highlighting the number of patients from each study with ROS1+ NSCLC, and the number of patients from each study included in the ROS1+ NSCLC efficacy population.

Please see Table 2 for the number of patients included in the primary efficacy set who received a dose of 600mg entrectinib.

Please see Table 3, Table 4, Table 5 and Table 6 for a more detailed breakdown of the dosing received by the patient population in each study.

Table 1: Populations by Study

Category	ALKA-372-001	RXDX-101-01	RXDX-101-02	RXDX-101-03	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	0	15	0	15
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: not dosed	1	0	1	0	2
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROS1+ NCSLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Prior ROS1 inhib	0	10	17	0	27
--Excluded: Other	0	0	4	0	4
ROS1+ NCSLC Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Non-Measurable Disease (>12m FUP)	2	1	0	0	3
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	6	0	6
ROS1+ NCSLC Efficacy Evaluable (explore)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Category	ALKA-372-001	RXDX-101-01	RXDX-101-02	RXDX-101-03	TOTAL
-Enrolled prior April 30, 2017 (>12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled after April 30, 2017 (<12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Dosing by Study (Efficacy Evaluable Population)

Schedule	ALKA-372-001	RXDX-101-01	RXDX-101-02	TOTAL
RXDX-101 600 mg/day (At RP2D)		[redacted]	[redacted]	[redacted]
RXDX-101 600 mg/day (F2) (At RP2D)		1		1
RXDX-101 by BSA 600 mg/day or 800 mg/day (Above RP2D)		1		1
Schedule A (Above RP2D)	2			2
Schedule B (Above RP2D)	1			1
Schedule B (At RP2D)	3			3
Schedule B (Below RP2D)	1			1
Schedule C (At RP2D)	1			1
Schedule C (Below RP2D)	1			1
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: ALKA-372-001 population dosing schedule

Category	Not Treated	Schedule A	Schedule B	Schedule C	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	0	0	0	0
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: not dosed	1	0	0	0	1
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROS1+ NCSLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Prior ROS1 inhib	0	0	0	0	0
--Excluded: Other	0	0	0	0	0
ROS1+ NCSLC Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Category	Not Treated	Schedule A	Schedule B	Schedule C	TOTAL
--Excluded: Non-Measurable Disease (>12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	0	0	0
ROS1+ NCSLC Efficacy Evaluable (explore)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled prior April 30, 2017 (>12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled after April 30, 2017 (<12m FUP)	0	0	0	0	0

Table 4: RXDX-101-01 population dosing schedule

Category	RXDX-101 100 mg/m2	RXDX-101 200 mg/m2	RXDX-101 400 mg/m2	RXDX-101 600 mg/day	RXDX-101 600 mg/day (F2)	RXDX-101 800 mg/day	RXDX-101 by BSA 600 mg/day or 800 mg/day	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	0	0	0	0	0	0	0
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: not dosed	0	0	0	0	0	0	0	0
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROS1+ NCSLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Prior ROS1 inhib	0	0	1	1	6	1	1	10
--Excluded: Other	0	0	0	0	0	0	0	0
ROS1+ NCSLC Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Non-Measurable Disease (>12m FUP)	0	0	0	0	1	0	0	1

Category	RXDX-101 100 mg/m2	RXDX-101 200 mg/m2	RXDX-101 400 mg/m2	RXDX-101 600 mg/day	RXDX-101 600 mg/day (F2)	RXDX-101 800 mg/day	RXDX-101 by BSA 600 mg/day or 800 mg/day	TOTAL
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	0	0	0	0	0	0
ROS1+ NCSLC Efficacy Evaluable (explore)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled prior April 30, 2017 (>12m FUP)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled after April 30, 2017 (<12m FUP)	0	0	0	0	0	0	0	0

Table 5: RXDX-101-02 population dosing schedule

Category	Not Treated	NOT TREATED	RXDX-101 600 mg/day	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	15	0	15
Enrolled	1	0	[redacted]	[redacted]
--Excluded: not dosed	1	0	0	1
Safety population	0	0	[redacted]	[redacted]
ROS1+ NCSLC	0	0	[redacted]	[redacted]
--Excluded: Prior ROS1 inhib	0	0	[redacted]	[redacted]
--Excluded: Other	0	0	[redacted]	[redacted]
ROS1+ NCSLC Efficacy	0	0	[redacted]	[redacted]
--Excluded: Non-Measurable Disease (>12m FUP)	0	0	0	0

Category	Not Treated	NOT TREATED	RXDX-101 600 mg/day	TOTAL
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	6	6
ROS1+ NCSLC Efficacy Evaluable (explore)	0	0	[redacted]	[redacted]
-Enrolled prior April 30, 2017 (>12m FUP)	0	0	[redacted]	[redacted]
-Enrolled after April 30, 2017 (<12m FUP)	0	0	[redacted]	[redacted]

Table 6: RXDX-101-03 population dosing schedule

Category	Part A 250 mg/m**2 (Escalation)	Part A 400 mg/m**2 (Escalation)	Part A 550 mg/m**2 (Escalation)	Part A 750 mg/m**2 (Escalation)	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	0	0	0	0
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: not dosed	0	0	0	0	0
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROS1+ NCSLC	0	0	0	0	0
--Excluded: Prior ROS1 inhib	0	0	0	0	0
--Excluded: Other	0	0	0	0	0
ROS1+ NCSLC Efficacy	0	0	0	0	0
--Excluded: Non-Measurable Disease (>12m FUP)	0	0	0	0	0
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	0	0	0
ROS1+ NCSLC Efficacy Evaluable (explore)	0	0	0	0	0
-Enrolled prior April 30, 2017 (>12m FUP)	0	0	0	0	0

Category	Part A 250 mg/m**2 (Escalation)	Part A 400 mg/m**2 (Escalation)	Part A 550 mg/m**2 (Escalation)	Part A 750 mg/m**2 (Escalation)	TOTAL
-Enrolled after April 30, 2017 (<12m FUP)	0	0	0	0	0

A3. Priority: The ERG's preferred efficacy set includes all patients with ROS1+ NSCLC and measurable disease at baseline who received 600 mg entrectinib in ALKA, STARTRK-1 and STARTRK-2, irrespective of response or follow-up duration. Please provide the following for this population:

After further clarification with the ERG, it was agreed that the ERGs preferred efficacy set will include patients from STARTRK-2 (who received 600mg entrectinib dosing from the start of the study) with measurable disease at baseline, irrespective of response or follow-up duration. Data are provided based on patients enrolled up to 31 May 2018 with a clinical cut-off date (CCOD) of 30 October 2018.

[redacted]

a) **A CONSORT diagram detailing the number of patients in this population, with reasons for ineligibility broken down by study;**

Please see the Table 1 in response to Question A2.

b) **The status of eligible patients for each study individually and overall at the 30 October 2018 clinical cut-off date (CCOD; e.g. number still on treatment, progressed, died, withdrawn from study);**

Table 7: Summary of patient status at CCOD, ERG Preferred Efficacy Set (N = 78)

Study	Status				n patients	% patients
RXDX-101-02	On treatment	Censored for PFS	On Study	Censored for OS	[redacted]	[redacted]
RXDX-101-02	Completed treatment	Progressed	Discontinued Study	Died	[redacted]	[redacted]
RXDX-101-02	Completed treatment	Progressed	On Study	Censored for OS	[redacted]	[redacted]
RXDX-101-02	On treatment	Progressed	On Study	Censored for OS	[redacted]	[redacted]
RXDX-101-02	Completed treatment	Censored for PFS	On Study	Censored for OS	[redacted]	[redacted]
RXDX-101-02	Completed treatment	Progressed	Discontinued Study	Censored for OS	[redacted]	[redacted]
RXDX-101-02	Completed treatment	Censored for PFS	Discontinued Study	Censored for OS	[redacted]	[redacted]

c) Mean and median follow-up at the 30 October 2018 CCOD for each study and overall;

Table 8: Summary of duration of follow-up at CCOD, ERG Preferred Efficacy Set (N=78)

Study	Mean FUP	Median FUP	Median FUP using inverse KM
RXDX-101-02	[redacted]	[redacted]	[redacted]

d) Baseline characteristics for each study individually and overall (as for Document B, Table 5);

Please note, in the original submission we presented the IQ range for baseline characteristics, whereas in Table 9 the range refers to the minimum and maximum values.

Table 9: Summary of baseline demographics, ERG Preferred Efficacy Set (N=78)

Study	Characteristic	Statistic/Category	Result
RXDX-101-02	Baseline Age	n	78
		mean	53.3

Study	Characteristic	Statistic/Category	Result
		median	53
		range	28 - 86
	Age Group 2	18-64	62 (79.5%)
		65-74	14 (17.9%)
		>=75	2 (2.6%)
	Sex	F	49 (62.8%)
		M	29 (37.2%)
	Race	ASIAN	36 (46.2%)
		WHITE	35 (44.9%)
		BLACK OR AFRICAN AMERICAN	5 (6.4%)
		NOT REPORTED	2 (2.6%)
	Baseline ECOG	1	38 (48.7%)
		0	30 (38.5%)
		2	10 (12.8%)
	Patient have a History of Smoking	N	44 (56.4%)
		Yes	34 (43.6%)
	Histology	ADENOCARCINOMA	76 (97.4%)
		BRONCHIOLOALVEOLAR CARCINOMA	1 (1.3%)
		CARCINOMAS WITH PLEOMORPHIC, SARCOMATOID, OR SARCOMATOUS ELEMENTS	1 (1.3%)
	Time Since Diagnosis (Months)	n	78
		mean	20.7
		median	7
		range	0.7 - 200.4
	Stage at Initial Diagnosis	IV	57 (73.1%)

Study	Characteristic	Statistic/Category	Result
		IIIA	8 (10.3%)
		IIIB	4 (5.1%)
		IB	3 (3.8%)
		IA	2 (2.6%)
		IIA	1 (1.3%)
		IIB	1 (1.3%)
		IIIC	1 (1.3%)
		UNKNOWN	1 (1.3%)
	Extent of Disease	METASTATIC DISEASE	77 (98.7%)
		LOCALLY ADVANCED	1 (1.3%)
	Bone Metastasis at Enrollment	Yes	33 (42.3%)
	Brain Metastasis at Enrollment	Yes	35 (44.9%)
	Liver Metastasis at Enrollment	Yes	18 (23.1%)
	Lung Metastasis at Enrollment	Yes	39 (50%)
	Lymph Node Metastasis at Enrollment	Yes	60 (76.9%)
	Other Metastasis Site at Enrollment	Yes	25 (32.1%)
	Gene Fusion Status	ROS1	78 (100%)
	Baseline CNS lesions by investigator	Absent	43 (55.1%)
		Present (not measurable)	27 (34.6%)
		Present (Measurable)	8 (10.3%)
	Any Prior Systemic Therapy	Yes	57 (73.1%)
	Prior Chemotherapy	Yes	54 (69.2%)
	Prior Immunotherapy	Yes	13 (16.7%)
	Prior Targeted Therapy	Yes	10 (12.8%)
	Prior Hormonal Therapy	Yes	1 (1.3%)
	Number of prior systemic therapies	0	31 (39.7%)

Study	Characteristic	Statistic/Category	Result
		1	30 (38.5%)
		>=3	9 (11.5%)
		2	8 (10.3%)

e) Results tables for primary and secondary efficacy endpoints (at the 30 October 2018 CCOD) equivalent to Document B Tables 7 to 13;

Table 10: Summary of Efficacy (ORR, DOR, PFS, CPFS, OS), ERG Preferred Set (N=78)

Study	Endpoint	Statistic/Category	Result
RXDX-101-02	Response (BICR)	Rate n, %	[redacted]
		95% CI for Rate	[redacted]
		PR	[redacted]
		CR	[redacted]
		PD	[redacted]
		SD	[redacted]
		NON CR/PD	[redacted]
		NE	[redacted]
	Duration of Response (BICR) (months)	Censored	[redacted]
		First Event: Disease Progression	[redacted]
		First Event: Death	[redacted]
		KM Median (95 % CI)	[redacted]
	Progression Free Survival (BICR) (months)	Censored	[redacted]
		First Event: Disease Progression	[redacted]
		First Event: Death	[redacted]
		KM Median (95 % CI)	[redacted]
	CNS Progression Free Survival (months)	Censored	[redacted]

Study	Endpoint	Statistic/Category	Result
		First Event: Death	[redacted]
		First Event: Disease Progression	[redacted]
		First Event: First New Lesion in CNS	[redacted]
		KM Median (95 % CI)	[redacted]
	Overall Survival (months)	Censored	[redacted]
		First Event: Death	[redacted]
		KM Median (95 % CI)	[redacted]

Table 11: QoL scores from baseline to end of treatment, ERG Preferred Set (N=78)

Questionnaire	Score	statistic	Baseline	End of Treatment	Change from baseline
EORTC QLQ-C30	Global Health Status	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Functional Scales - Physical Functioning (revised)	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Functional Scales - Role Functioning (revised)	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Functional Scales - Cognitive Functioning	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Symptom Scales - Dyspnoea	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Symptom Scales - Fatigue	Mean (sd)	[redacted]	[redacted]	[redacted]

Questionnaire	Score	statistic	Baseline	End of Treatment	Change from baseline
		Median (range)	[redacted]	[redacted]	[redacted]
EORTC QLQ-LC13	Coughing	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Dyspnoea	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Pain in arm or shoulder	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Pain in chest	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]
	Pain in other parts	Mean (sd)	[redacted]	[redacted]	[redacted]
		Median (range)	[redacted]	[redacted]	[redacted]

f) Kaplan-Meier (KM) data in Excel format with number of patients at risk for overall survival (OS), progression-free survival (PFS) and time to central nervous system (CNS) progression (30 October 2018 CCOD);

Please find KM data requested in Appendix B.

g) Mean time on treatment, mean number of cycles received and mean dose received at the 30 October 2018 CCOD for each study and overall;

Table 12: Summary of Entrectinib Exposure, ERG Preferred Efficacy Set (N=78)

Study	Endpoint	Statistic/Category	Result
RXDX-101-02	Number of Cycles received	n	[redacted]
		mean	[redacted]
		median	[redacted]
		range	[redacted]
	Total cumulative dose (mg)	n	[redacted]
		mean	[redacted]
		median	[redacted]
		range	[redacted]
	Treatment duration (months)	n	[redacted]
		mean	[redacted]
		median	[redacted]
		range	[redacted]

h) A table detailing the number and proportion of patients who had received prior cancer therapies for each study individually and overall, broken down by class (platinum therapy, TKI, immunotherapy, chemotherapy), and drug (example format below).

Table 13: Summary of prior systemic therapy, ERG Preferred Efficacy Set (N=78)

WHO ATC Level 4	Generic name	n patients	% patients
PLATINUM COMPOUNDS	Any	[redacted]	[redacted]
PLATINUM COMPOUNDS	CISPLATIN	[redacted]	[redacted]
PLATINUM COMPOUNDS	CARBOPLATIN	[redacted]	[redacted]
FOLIC ACID ANALOGUES	Any	[redacted]	[redacted]
FOLIC ACID ANALOGUES	PEMETREXED	[redacted]	[redacted]
FOLIC ACID ANALOGUES	PEMETREXED DISODIUM	[redacted]	[redacted]
FOLIC ACID ANALOGUES	PEMETREXED DISODIUM HEPTAHYDRATE	[redacted]	[redacted]
MONOCLONAL ANTIBODIES	Any	[redacted]	[redacted]
MONOCLONAL ANTIBODIES	NIVOLUMAB	[redacted]	[redacted]
MONOCLONAL ANTIBODIES	BEVACIZUMAB	[redacted]	[redacted]

WHO ATC Level 4	Generic name	n patients	% patients
MONOCLONAL ANTIBODIES	LAMBROLIZUMAB	[redacted]	[redacted]
MONOCLONAL ANTIBODIES	ANETUMAB RAVTANSINE	[redacted]	[redacted]
TAXANES	Any	[redacted]	[redacted]
TAXANES	PACLITAXEL	[redacted]	[redacted]
TAXANES	DOCETAXEL	[redacted]	[redacted]
TAXANES	PACLITAXEL ALBUMIN	[redacted]	[redacted]
PYRIMIDINE ANALOGUES	Any	[redacted]	[redacted]
PYRIMIDINE ANALOGUES	GEMCITABINE	[redacted]	[redacted]
PYRIMIDINE ANALOGUES	GEMCITABINE HYDROCHLORIDE	[redacted]	[redacted]
PYRIMIDINE ANALOGUES	GIMERACIL W/OTERACIL POTASSIUM/TEGAFUR	[redacted]	[redacted]
PYRIMIDINE ANALOGUES	UFTORAL	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	Any	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	ERLOTINIB HYDROCHLORIDE	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	CRIZOTINIB	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	ERLOTINIB	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	AFATINIB	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	GEFITINIB	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	NINTEDANIB	[redacted]	[redacted]
PROTEIN KINASE INHIBITORS	TIVANTINIB	[redacted]	[redacted]
PODOPHYLLOTOXIN DERIVATIVES	Any	[redacted]	[redacted]
PODOPHYLLOTOXIN DERIVATIVES	ETOPOSIDE	[redacted]	[redacted]
OTHER ANTINEOPLASTIC AGENTS	Any	[redacted]	[redacted]
OTHER ANTINEOPLASTIC AGENTS	OTHER ANTINEOPLASTIC AGENTS	[redacted]	[redacted]
OTHER ANTINEOPLASTIC AGENTS	TOPOTECAN HYDROCHLORIDE	[redacted]	[redacted]
VINCA ALKALOIDS AND ANALOGUES	Any	[redacted]	[redacted]
VINCA ALKALOIDS AND ANALOGUES	VINORELBINE	[redacted]	[redacted]
OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZ	Any	[redacted]	[redacted]

WHO ATC Level 4	Generic name	n patients	% patients
OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZ	DENOSUMAB	[redacted]	[redacted]
OTHER THERAPEUTIC PRODUCTS	Any	[redacted]	[redacted]
OTHER THERAPEUTIC PRODUCTS	INVESTIGATIONAL DRUG	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	Any	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]
ANTHRACYCLINES AND RELATED SUBSTANCES	Any	[redacted]	[redacted]
ANTHRACYCLINES AND RELATED SUBSTANCES	AMRUBICIN HYDROCHLORIDE	[redacted]	[redacted]
AROMATASE INHIBITORS	Any	[redacted]	[redacted]
AROMATASE INHIBITORS	LETROZOLE	[redacted]	[redacted]
COMBINATIONS OF ANTINEOPLASTIC AGENTS	Any	[redacted]	[redacted]
COMBINATIONS OF ANTINEOPLASTIC AGENTS	CARBOPLATIN W/GEMCITABINE	[redacted]	[redacted]

Subgroup analysis

A4. Priority: Please use the ERG's preferred efficacy set defined in A3 to conduct a subgroup analysis to explore the impact of prior TKI use on overall response rate (ORR), OS and PFS (BICR). Please also provide results using the primary efficacy set if it remains your preferred population.

Please see Table 14 for a breakdown of the number of patients from the ERG's preferred efficacy set who received a prior TKI. Evidently, prior TKI use is a small subgroup of patients (n=10).

Table 15 highlights the impact of prior TKI use on ORR, OS and PFS. There is no statistically significant improvement in model fit by including prior-TKI use in the model. Furthermore, the effect sizes are small with no consistent trend across the endpoints.

Table 14: Prior TKI summary

Medicine name	n patients	% patients
Any protein kinase inhibitor	[redacted]	[redacted]
Erlotinib Hydrochloride	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]
Nintedanib	[redacted]	[redacted]
Tivantinib	[redacted]	[redacted]

Table 15: Subgroup analysis

Endpoint	No Prior TKI		Prior TKI		Prior TKI vs no prior TKI	
(model)	n patients	n events/ responses	n patients	n events/ responses	Effect estimate (OR/HR)	p-Value (LRT)
ORR (logistic regression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (cox model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (cox model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A5. Please provide primary and secondary efficacy results and intracranial outcomes for the subgroup of patients with CNS metastases at baseline in the

ERG's preferred efficacy set (in the same format as Document B, Table 14 and 15).

Please see Table 16 for the primary and secondary efficacy results for patients with CNS metastases at baseline, and Table 17 for the intracranial outcomes for patients with CNS metastases at baseline.

Table 16: Summary of Efficacy by CNS Disease Status, ERG Preferred Efficacy Set (N = 78)

Study	Endpoint	Statistic/Category	No (n=43)	Yes (n=35)
RXDX-101-02	Response (BICR)	Rate n, %	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	95% CI for Rate	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	PR	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	CR	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	NON CR/PD	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	SD	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	PD	[redacted]	[redacted]
RXDX-101-02	Response (BICR)	NE	[redacted]	[redacted]
RXDX-101-02	Duration of Response (BICR) (months)	Censored	[redacted]	[redacted]
RXDX-101-02	Duration of Response (BICR) (months)	First Event: Disease Progression	[redacted]	[redacted]
RXDX-101-02	Duration of Response (BICR) (months)	First Event: Death	[redacted]	[redacted]
RXDX-101-02	Duration of Response (BICR) (months)	KM Median (95 % CI)	[redacted]	[redacted]
RXDX-101-02	Progression Free Survival (BICR) (months)	Censored	[redacted]	[redacted]
RXDX-101-02	Progression Free Survival (BICR) (months)	First Event: Disease Progression	[redacted]	[redacted]
RXDX-101-02	Progression Free Survival (BICR) (months)	First Event: Death	[redacted]	[redacted]

Study	Endpoint	Statistic/Category	No (n=43)	Yes (n=35)
RXDX-101-02	Progression Free Survival (BICR) (months)	KM Median (95 % CI)	[redacted]	[redacted]
RXDX-101-02	Overall Survival (months)	Censored	[redacted]	[redacted]
RXDX-101-02	Overall Survival (months)	First Event: Death	[redacted]	[redacted]
RXDX-101-02	Overall Survival (months)	KM Median (95 % CI)	[redacted]	[redacted]

Table 17: Overview of Intracranial Efficacy in Patients with Baseline CNS Disease Status, ERG Preferred Efficacy Set (N = 78)

Study	Endpoint	Statistic/Category	Patients with Baseline CNS Disease (n=31)
RXDX-101-02	Intracranial Response	Rate n, %	[redacted]
RXDX-101-02	Intracranial Response	95% CI for Rate	[redacted]
RXDX-101-02	Intracranial Response	PR	[redacted]
RXDX-101-02	Intracranial Response	NON CR/PD	[redacted]
RXDX-101-02	Intracranial Response	CR	[redacted]
RXDX-101-02	Intracranial Response	PD	[redacted]
RXDX-101-02	Duration of Intracranial Response (months)	Censored	[redacted]
RXDX-101-02	Duration of Intracranial Response (months)	First Event: Disease Progression	[redacted]
RXDX-101-02	Duration of Intracranial Response (months)	First Event: Death	[redacted]
RXDX-101-02	Duration of Intracranial Response (months)	KM Median (95 % CI)	[redacted]
RXDX-101-02	Intracranial Progression Free Survival (months)	Censored	[redacted]
RXDX-101-02	Intracranial Progression Free Survival (months)	First Event: Disease Progression	[redacted]
RXDX-101-02	Intracranial Progression Free Survival (months)	First Event: Death	[redacted]

Study	Endpoint	Statistic/Category	Patients with Baseline CNS Disease (n=31)
RXDX-101-02	Intracranial Progression Free Survival (months)	KM Median (95 % CI)	[redacted]

Indirect treatment comparison

A6. Priority: Please conduct an alternative MAIC for entrectinib versus crizotinib using the ERG's preferred efficacy set for the entrectinib integrated analysis (30 October 2018 CCOD) and the more mature PROFILE 1001 data from Shaw 2019 (reference 48). Please provide results for all endpoints previously provided for the original MAIC (OS, PFS, ORR, any SAE, any Grade 3+ AE, treatment discontinuation due to AE) and follow the NICE DSU recommendations for unanchored matching adjusted indirect comparisons (Technical Support Document 18), specifically:

a) **Adjust for all effect modifiers and prognostic variables (TSD18, Section 4.2.5)**

An alternative MAIC using the ERG's preferred efficacy set for the entrectinib integrated analysis (30 October 2018 CCOD) and the more mature PROFILE 1001 data from Shaw 2019 has been conducted as requested.

The approach taken to the MAIC was as per the original MAIC and therefore as previously described. For the comparison of entrectinib with PROFILE 1001 crizotinib, the final baseline characteristics selected for matching were sex, race (Asian vs. non-Asian), ECOG (0 vs. 1 or 2), smoking history, prior treatments (treatment naïve vs. prior treatment), and age. The original and weighted patient characteristics are summarised in Table 18.

Table 18: Baseline characteristics included in estimation of MAIC weights for comparison of entrectinib versus PROFILE 1001 crizotinib

Intervention	ESS	Female	Asian	ECOG 2	Never smoke	Treatment naïve	Age
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib Re-weighted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib	53	56.6	39.6	1.9	75.5	13.2	55

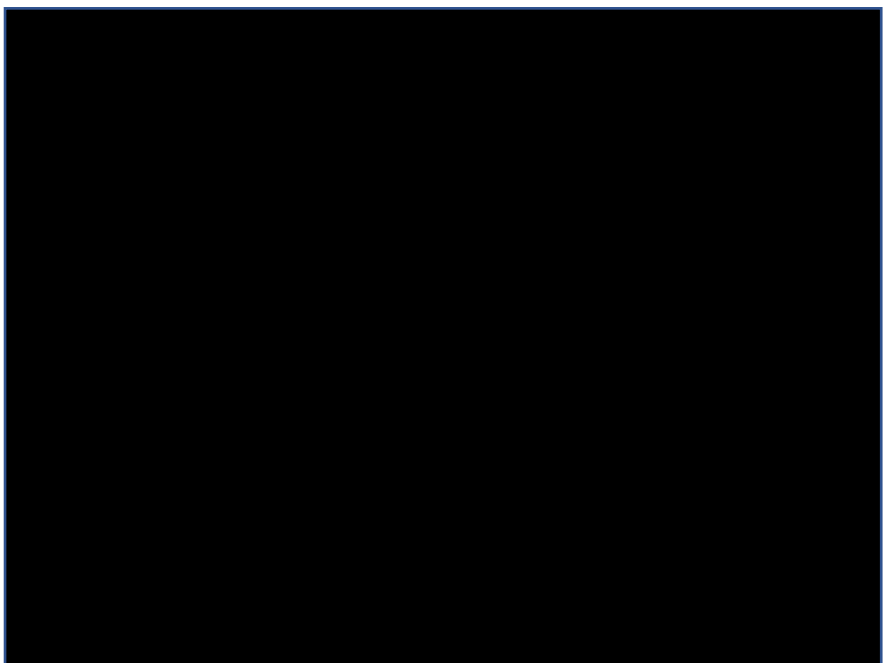
Key: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size.
Note: Age is mean for entrectinib, median for crizotinib.

Results for most endpoints previously provided for the original MAIC (OS, PFS [BICR and IA] and ORR) are provided in Figure 1 to Figure 3 and Table 19. An alternative MAIC for discontinuation due to AEs has not been conducted as the safety population were used for the original MAIC and there are no updates to this outcome reported in the more mature PROFILE 1001 data from Shaw 2019.

Figure 1: Kaplan–Meier Plot of OS – entrectinib versus crizotinib

Key: HR, hazard ratio; OS, overall survival.

Figure 2: Kaplan–Meier Plot of PFS BICR – entrectinib versus crizotinib



Key: BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

Figure 3: Kaplan–Meier Plot of PFS IA – entrectinib versus crizotinib

Table 19: Summary of ORR – entrectinib versus crizotinib

Intervention	Comparator	Sample Size	Number with ORR	% with ORR	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Crizotinib		53	38	71.7	

Key: CI, confidence interval; MAIC, matching adjusted indirect comparison; ORR, objective response rate.

b) Consider methods to quantify systematic error (TSD18, Appendix C)

We have considered methods to quantify systemic error, in accordance with TSD18 and agree that this is an important area for further research. Unfortunately, in this case we do not believe standard methods for quantifying systemic error can be applied. To talk to those specifically referenced in Appendix C of TSD18:

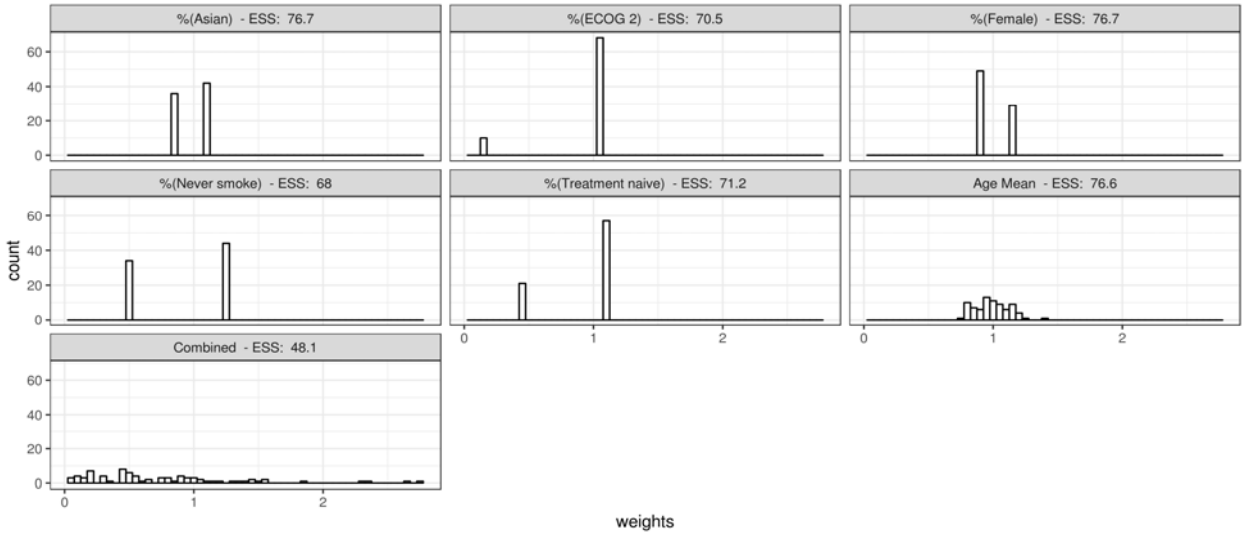
> C1.1) The out of sample method requires a set of studies in the target population, while in this case we have a limited set of studies in ROS1 NSCLC to estimate the between study variance.
>
> C1.2) Given we apply a MAIC and not STC approach, the in-sample cross validation method cannot be applied.

We should note that the selection of covariates adjusted for were validated based on medical expertise on what important prognostic and effect modifiers apply and the inherent limitations on how many variables can be reasonably adjusted for across the small sample sizes providing evidence in the ROS1 NSCLC setting.

c) Present the distribution of estimated weights and effective sample size (ESS) individually for each adjusted variable.

Figure 4 highlights the estimated weights and effective sample size matched for each adjusted individual variable. Combined is the distribution of weights and ESS when matching on all variables.

Figure 4: Distribution of weights and ESS for all variables, PROFILE 1001



A7. Priority: Please conduct an alternative MAIC for entrectinib versus pemetrexed plus platinum therapy using the ERG's preferred efficacy set for the entrectinib integrated analysis (30 October 2018 CCOD) and ASCEND-4 (following the methods and outputs set out in A6 a), b) and c)).

a) Adjust for all effect modifiers and prognostic variables (TSD18, Section 4.2.5)

An alternative MAIC using the ERG's preferred efficacy set for the entrectinib integrated analysis (30 October 2018 CCOD) and ASCEND-4 has been conducted as requested.

The approach taken to the MAIC was as per the original MAIC and therefore as previously described. For the comparison of entrectinib with ASCEND-2 pemetrexed plus platinum, the final baseline characteristics selected for matching were sex, race (Asian vs. non-Asian), ECOG (0 vs. 1 or 2), smoking history, age and disease stage (Stage IIIB vs. Stage IV non-CNS metastasis vs. Stage IV CNS metastasis). The original and weighted patient characteristics are summarised in Table 20.

Table 20: Baseline characteristics included in estimation of MAIC weights for comparison of entrectinib versus ASCEND-4 pemetrexed plus platinum

Intervention	ESS	Female	Asian	ECOG 2	Never smoke	Age	Disease stage
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

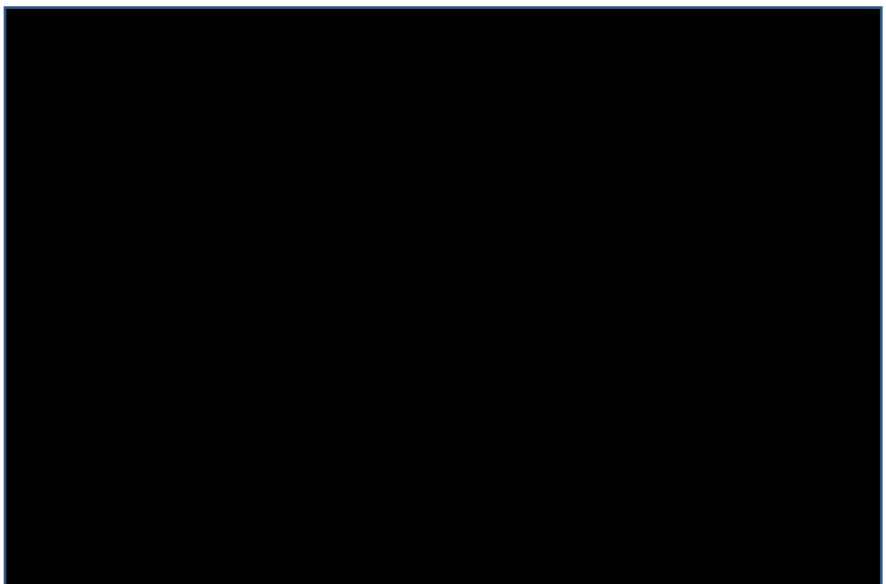
Entrectinib Re-weighted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed plus platinum	187	61.0	43.9	5.9	65.2	54	IIIB: 2.7 IV-CNS: 33.2
Key: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size. **Note**: Age is mean for entrectinib, median for crizotinib.							

Results for most endpoints previously provided for the original MAIC (OS, PFS [BICR], ORR) are provided in Figure 5, Figure 6 and Table 21. An alternative MAIC for discontinuation due to AEs has again not been conducted as the safety population were used for the original MAIC.

Figure 5: Kaplan–Meier Plot of OS – entrectinib versus pem/plat

Key: HR, hazard ratio; OS, overall survival; pem/plat, pemetrexed plus platinum.

Figure 6: Kaplan–Meier Plot of PFS BICR – entrectinib versus pem/plat



Key: BICR, blinded independent central review; HR, hazard ratio; pem/plat, pemetrexed plus platinum; PFS, progression-free survival.

Table 21: Summary of ORR – entrectinib versus pem/plat

Intervention	Comparator	Sample Size	Number with ORR	% with ORR	Odds Ratio (95% CI)
Entrectinib Re-Weighted MAIC	Pemetrexed plus platinum	[redacted]	[redacted]	[redacted]	[redacted]
Entrectinib unadjusted		[redacted]	[redacted]	[redacted]	
Pemetrexed plus platinum		187	50	26.7	

Key: CI, confidence interval; MAIC, matching adjusted indirect comparison; ORR, objective response rate; pem/plat, pemetrexed plus platinum.

b) Consider methods to quantify systematic error (TSD18, Appendix C)

We have considered methods to quantify systemic error, in accordance with TSD18 and agree that this is an important area for further research. Unfortunately, in this case we do not believe standard methods for quantifying systemic error can be applied. To talk to those specifically referenced in Appendix C of TSD18:

> C1.1) The out of sample method requires a set of studies in the target population, while in this case we have a limited set of studies in ROS1 NSCLC to estimate the between study variance.
>
> C1.2) Given we apply a MAIC and not STC approach, the in-sample cross validation method cannot be applied.

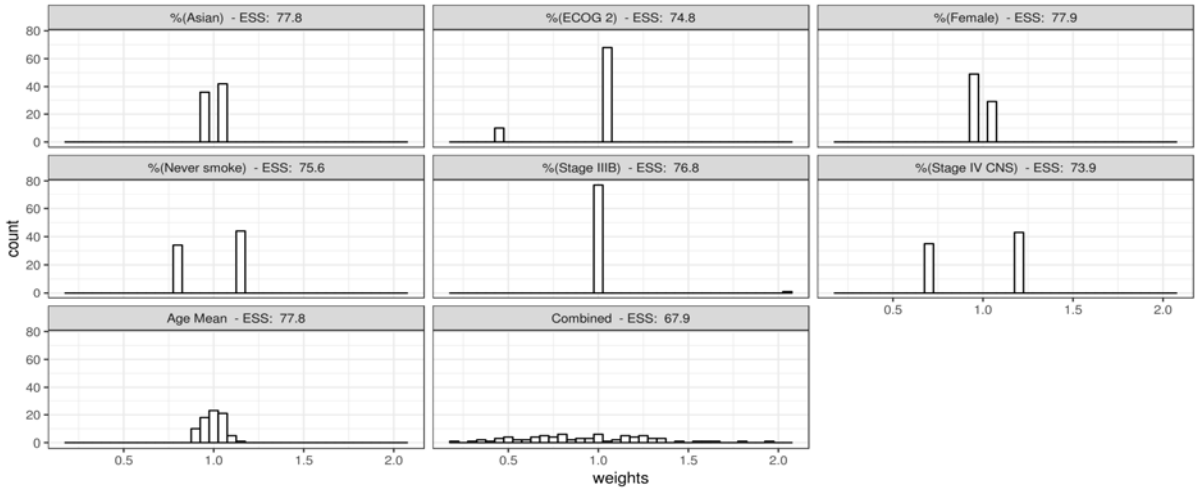
We should note that the selection of covariates adjusted for were validated based on medical expertise on what important prognostic and effect modifiers apply and the

inherent limitations on how many variables can be reasonably adjusted for across the small sample sizes providing evidence in the ROS1 NSCLC setting.

c) **Present the distribution of estimated weights and effective sample size individually for each adjusted variable**

Figure 7 highlights the estimated weights and effective sample size matched for each adjusted individual variable. Combined is the distribution of weights and ESS when matching on all variables.

Figure 7: Distribution of weights and ESS for all variables, ASCEND 4



A8. Priority: Please present an assessment of proportional hazards for PFS and crossover-adjusted OS in PROFILE 1014 to justify the chosen method used to derive comparative estimates for pemetrexed plus platinum therapy.

This was considered during technology appraisal (TA) 406 in which the following was noted by the manufacturer in response to ERG questions B11 and B13:

An assumption of proportional hazards was assessed by inspecting the plot of log hazards by log time for PFS and OS. In general, the plots did not yield large departures from the parallel lines, therefore the assumption of a constant treatment effect was made for both analyses. The proportional hazards assumption was discussed with a UK clinical expert with experience treating ALK-positive patients with both crizotinib and chemotherapy. The expert stated that it was clinically reasonable to assume proportional hazards.

The committee did have concerns with this in TA406 and similar concerns on the proportional hazard assumption were recognised in TA529. However, the chosen method used to derive comparative estimates for pemetrexed plus platinum therapy is still considered to be the most appropriate option considering the limitations of the evidence base available.

As discussed in the company submission, there are no data available for pemetrexed plus platinum therapy in the ROS1 population. In any indirect comparisons for entrectinib versus pemtrexed plus platinum therapy an assumption of general comparability across the ROS1 and ALK+ populations is needed (as was the case in the MAIC presented). In applying the PROFILE 1014 outcomes to the crizotinib arm of the model this assumption is replaced with an assumption that the relative treatment effect of crizotinib and pemetrexed plus platinum therapy is equivalent across the ROS1 and ALK+ populations. Such an assumption was accepted in technology appraisal TA529 and therefore was used in the base case model. However, in recognition of the limitations of both approaches, the MAIC used to derive comparative estimates for pemetrexed plus platinum therapy (using integrated analysis for entrectinib [primary efficacy set in original company model] and ASCEND-4 data for pemetrexed plus platinum) was used in a scenario analysis. With either approach entrectinib was shown to be cost-effective.

A9. Priority: If the existing entrectinib integrated analysis based on the primary efficacy set remains your preferred population for the MAICs, please provide:

a) **Mean time on treatment, mean number of cycles received and mean dose received for each entrectinib study individually and overall (30 October 2018 CCOD);**

b) **Time to CNS progression as presented in Table 10 (30 October 2018 CCOD), with underlying KM data;**

c) **The table proposed for A3 h) detailing the proportion of patients who had received prior therapies, broken down by class and type of drug;**

d) **Updated MAICs following the methods and outputs outlined in A6 a), b) and c) and using results from the 30 October 2018 CCOD for the entrectinib integrated analysis.**

We will be providing alternative MAICs using the ERG's preferred efficacy set and therefore this question is redundant.

A10. Priority: If prior TKI use is shown to have an impact on outcomes as a result of the subgroup analysis requested in A4, please consider scenario analyses for the MAIC requested in A6 excluding patients from the entrectinib population who had received prior TKI.

Prior TKI use was not shown to have an impact on outcomes and therefore a scenario analyses for the MAIC based on this factor is not required.

Literature searching

A11. Please provide summary study characteristics (primary reference, study design, population, prior treatment, intervention, comparator, key endpoints, median follow-up) for:

a) **the 11 studies that met the inclusion criteria for the ROS1 systematic literature review (SLR);**

b) **the 34 studies that met the inclusion criteria for the original ALK+ NSCLC SLR (Appendix D.1, Figure 2);**

c) **the 25 studies that met the inclusion criteria for the update ALK+ NSCLC SLR.**

The requested summary data is provided in Table 22, Table 23 and Table 24.

Table 22: Summary study characteristics for the 11 studies that met the inclusion criteria for the ROS1 SLR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
PROFILE 1001 (NCT00585195)	Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014; 371(21):1963-71.	Phase I, open-label, single arm, multicentre study	ROS1 +ve	86% had received ≥1 previous standard therapy for advanced NSCLC	Crizotinib	N/A	RR DoR TTR PFS OS Safety	16.4 months for OS
OX-ONC (NCT01945021)	Wu YL, Yang JCH, Kim DW, et al. Phase II study of crizotinib in east Asian patients with ROS1-positive advanced non–small-cell lung cancer. Journal of Clinical Oncology. 2018; 36(14):1405-11.	Phase II, open-label, single arm, multicentre study	ROS1 +ve ALK -ve	≤3 lines of prior systemic therapies for advanced-stage disease	Crizotinib	N/A	ORR by IRR DoR TTR DCR PFS OS Safety PROs	21.4 months for OS
METROS trial (NCT02499614)	Landi L, Chiari R, Dazzi C, et al. Crizotinib in ROS1 rearranged or met deregulated non-small-cell lung cancer (NSCLC): Final results of the metros trial. Journal of Thoracic Oncology. 2017; 12(11):S1898.	Phase II, open-label, single arm, multicentre study	ROS1 +ve	≥1 previous standard chemotherapy regimen	Crizotinib	N/A	RR PFS OS Safety	NR
ACSe trial (NCT02034981)	Moro-Sibilot D, Cozic N, Pérol M, et al. Activity of Crizotinib in MET or ROS1	Phase II, open-label, single arm,	ROS1 +ve	≥1 standard treatment (including a platinum-	Crizotinib	N/A	RR DoR PFS	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Positive (+) NSCLC: Results of the AcSé Trial. Journal of Thoracic Oncology. 2018; 13(10):S348.	multicentre study		based doublet, unless pts were considered as unfit for chemotherapy)			OS	
EUROS1	Mazières J, Rouvière D, J DM, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: Results from the EUROS1 cohort. Journal of Clinical Oncology. 2015; 33(9):992-9	Retrospective, observational, multicentre study	ROS1 +ve	ROS +ve / MET amplification ≥1 previous standard chemotherapy regimen	Crizotinib	N/A	RR PFS OS Safety	NR
Bennati 2015	Bennati C, Chiari R, Marcomigni L, et al. ROS1 rearrangement in lung adenocarcinoma: A retrospective cohort study. Annals of Oncology. 2015; 26.	Retrospective, observational study	ROS1 +ve	ROS +ve Progression after at ≥1 standard treatment (including a platinum-based doublet, unless pts were considered as unfit for chemotherapy)	Crizotinib	N/A	Tumour responses PFS OS	NR
Zhang 2016	Zhang L, Jiang T, Zhao C, et al. Efficacy of crizotinib and pemetrexed-based	Retrospective, observational, single centre study	ROS1 +ve	Crizotinib; pemetrexed-based chemotherapy,	Crizotinib	N/A	RR ORR DCR	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. Oncotarget 2016; 7(46):75145-54.			non-pemetrexed-based chemotherapy			PFS	
Scheffler 2015	Scheffler M, Schultheis A, Teixido C, et al. ROS1 rearrangements in lung adenocarcinoma: Prognostic impact, therapeutic options and genetic variability. Oncotarget. 2015; 6(12):10577-85.	Retrospective, observational, single centre study	ROS1 +ve	Previous systemic chemotherapy	Crizotinib	N/A	Tumour responses OS	16.6 months for OS
Patil 2018	Patil T, Smith D, Bunn P, et al. The Incidence of Brain Metastases in ROS1-Rearranged Non-Small Cell Lung Cancer at Diagnosis and Following Progression on Crizotinib. Journal of Thoracic Oncology. 2018; 13(10):S492-S3.	Retrospective, observational, single centre study	ROS1 +ve	NR	Crizotinib	N/A	PFS CNS progression	130 weeks
Chen 2016	Chen YF, Hsieh MS, Wu SG, et al. Efficacy of pemetrexed-based chemotherapy in patients with ROS1 fusion-positive lung	Retrospective, observational, single centre study	ROS1 +ve	NR	Pemetrexed	Pemetrexed + Platinum Combination	Tumour responses PFS OS	14.1 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	adenocarcinoma compared with in patients harbouring other driver mutations in East Asian populations. Journal of Thoracic Oncology. 2016; 11(7):1140-52.							
Zhang 2018	Zhang B, Chu T, Xu J, et al. Efficacy of pemetrexed-based chemotherapy in advanced lung adenocarcinoma patients with ROS-1 rearrangement. Journal of Thoracic Oncology. 2018; 13(4):S100.	Retrospective, observational study	ROS1 +ve	Platinum-based dual agent chemotherapy as palliative treatment	Pemetrexed-containing (Pem-C)	Non-pemetrexed-containing (Non-Pem-C)	ORR PFS	NR

Table 23: Summary study characteristics for the 34 studies that met the inclusion criteria for the original ALK+ SLR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
ALEX (NCT02075840, 2013-004133-33, EudraCT Number)	Peters S, Camidge D, Shaw A, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2017; 377:829-38.	Phase III, open-label, RCT, multicentre study	ALK +ve	Treatment-naïve	Alectinib 300 mg bid taken with food	Crizotinib 25mg bid taken with or without food	PFS CNS progression OS ORR DoR Safety	18.6 months (alectinib) 17.6 months (crizotinib)

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
ALUR (NCT02604342)	Novello S, Mazieres J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018; 29(6):1409-16.	Phase III, open-label, RCT, multicentre study	ALK +ve	2 prior lines of systemic therapy, including 1 line of platinum-based doublet chemotherapy Crizotinib	Alectinib 600mg bid	Pemetrexed 500 mg/m2 every 3 weeks or docetaxel 75 mg/m2 every 3 weeks	Inv PFS CNS ORR PFS (BIRC) ORR DCR Inv DoR DoR (BICR) CND DCR OS Safety	6.5 months (alectinib) 5.8 months (chemotherapy)
ASCEND-4 (NCT01828099)	Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): A randomised, open-label, phase 3 study. The Lancet. 2017.	Phase III, open-label, RCT, multicentre study	ALK +ve	Untreated with any systemic anticancer therapy (except neoadjuvant or adjuvant systemic therapy [if relapse had occurred >12 months from the end of therapy]	Ceritinib 750mg qd orally	Cisplatin 75 mg/sqm every 3 weeks for 4 cycles or Carboplatin AUC 5-6 + pemetrexed 500 mg/sqm every 3 weeks for 4 cycles followed by pemetrexed maintenance	PFS (BICR) OS Inv PFS ORR DoR DCR time to response Intracranial ORR Intracranial DCR Intracranial DOR Intracranial CBR PROs Safety PK	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
ASCEND-5 (NCT01828112)	Shaw A, Kim T, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The lancet Oncology. 2017; 18:874-86.	Phase III, open-label, RCT, multicentre study	ALK +ve	Crizotonib and 1-2 lines of chemotherapy	Ceritinib 750mg qd	Pemetrexed 500 mg/m2 every 3 weeks or docetaxel 75 mg/m2 every 3 weeks	PFS (BICR) ORR (BICR) DCR (BICR) Inv PFS Inv ORR Inv DOR OS Safety PROs	16.5 months
J-ALEX (JapicCTI-132316)	Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet (London, England). 2017; 390:29-39.	Phase III, open-label, RCT, multicentre study	ALK +ve	ALK TKI naïve, chemotherapy naïve or 1 previous line of chemotherapy (64% treatment-naïve, 36% 1 previous chemotherapy)	Alectinib 300 mg bid orally	Crizotinib 250 mg bid orally	PFS (BIRC) Inv PFS OS ORR DoR TTR PROs Safety PK	12.0 months (alectinib) 12.2 months (crizotinib)
PROFILE 1007 (NCT00932893)	Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. New England Journal of	Phase III, open-label, RCT, multicentre study	ALK +ve	One prior platinum-based chemotherapy regimen Crizotinib-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 or Docetaxel 75 mg/m2	PFS (BIRC) OS ORR DoR TTR Safety PROs	12.2 months for OS

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Medicine. 2013;368(25):2385-94.							
PROFILE 1014 (NCT01154140)	Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine [Internet]. 2014; 371(23):[2167-77 pp.]	Phase III, open-label, RCT, multicentre study (crossover permitted following progression)	ALK +ve	Treatment-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 or carboplatin AUC 5-6mg/mL/min 3 wk cycle Max 6 cycles	PFS (BICR) ORR OS DoR TTR OS Safety PROs	17 months
PROFILE 1029, A8081029 (NCT01639001)	Wu YL, Lu S, Lu Y, et al. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018; 13(10):1539-48.	Phase III, open-label, RCT, multicentre study (crossover permitted following progression)	ALK +ve	Treatment-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 or carboplatin AUC 5-6mg/mL/min 3 wk cycle Max 6 cycles	PFS (BICR) ORR OS TTP Safety PROs	22.5 months (crizotinib) 21.6 months (chemotherapy) for OS
AF-001JP (JapicCTI-101264)	Tamura T, Kiura K, Seto T, et al. Three-year follow-up of an alectinib phase I/II study in ALK-positive non-small-cell lung cancer: aF-001JP. Journal of Clinical Oncology. 2017; 35(Issue):1515-21	Phase I/II, open-label, single arm, multicentre study	ALK +ve Japanese pts	≥1 prior chemotherapy regimens Crizotinib-naïve	Alectinib 300mg bid	N/A	ORR (IRC) DCR PFS OS PK Safety	3 years

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
AF-002JG (NCT01588028)	Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014; 15(10):1119-28.	Phase I/II, open-label, single arm, multicentre study	ALK +ve	Crizotinib (+/- chemotherapy)	Alectinib 300-900 mg bid (phase I) Alectinib 600 mg bid (phase II)	N/A	Establish recommended Phase II dose for alectinib Safety preliminary tumour response (RECIST v1.1) PK	126 days
ASCEND-2 (NCT01685060)	Crino L, Ahn MJ, De Marinis F, et al. Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2. J Clin Oncol. 2016; 34(24):2866-73.	Phase II, open-label, single arm, multicentre study	ALK +ve	≥2 previous treatment regimens including at least one platinum based chemotherapy and crizotinib	Ceritinib 750 mg qd	N/A	ORR (INV) Response (INV and BIRC) OS Safety PROs	11.3 months
ASCEND-3 (NCT01685138)	Felip E, Orlov S, Park K, et al. Phase 2 study of ceritinib in ALKi-naive patients (pts) with ALK-rearranged (ALK+) non-small cell	Phase II, open-label, single arm, multicentre study	ALK +ve	≤3 lines prior chemotherapy ALK inhibitor-naïve	Ceritinib 750 mg qd	N/A	ORR (INV) DOR DCR TTR	23.4 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	lung cancer (NSCLC): whole body responses in the overall pt group and in pts with baseline brain metastases (BM). Annals of oncology Conference: 41st european society for medical oncology congress, ESMO 2016 Denmark						ORR (BIRC), Safety PFS (BIRC or INV) OS Intracranial ORR	
ASCEND-6 (NCT02040870)	Zhang L, Shi, Y, Tan DSW, et al. ASCEND-6: single-arm, open label, multicenter phase ½ study of ceritinib in Chinese pts with advanced ALK rearranged (ALK1) non-small cell lung cancer (NSCLC) previously treated with crizotinib. ESMO Asia 2016 Congress. Annals of Oncology (2016) 27 (suppl_9): ix139-ix156. 10.1093/annonc/mdw594	Phase I/II, open-label, single arm, multicentre study	ALK +ve Chinese patients	Crizotinib ≤2 lines chemotherapy	Ceritinib 750 mg qd (fasted)	N/A	PK Safety and tolerability ORR (INV) DOR DCR TTR PFS (INV by RECIST v1.1) OS ORR (BIRC) Intracranial ORR (BICR)	8.3 months
CAUY922A220 (NCT01124864)	Felip E, Barlesi F, Besse B, et al. Phase 2 Study of the HSP-90 Inhibitor AUY922 in Previously Treated and Molecularly Defined Patients with Advanced Non-Small Cell Lung	Phase II, open-label, single arm, multicentre study	22/121 (18%) ALK+ve	≥2 prior lines of therapy	Luminespib 70 mg/m2 qw	N/A	Inv ORR OS PFS Safety	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Cancer. J Thorac Oncol. 2018; 13(4):576-84.							
AUY922 trial 12-458 (NCT01752400)	Gainor JF, Marcoux JP, Rabin M, Gandhi L, Costa DB, Logan J, et al. A phase ii trial of AUY922, a heat shock protein 90 (HSP90) inhibitor, in ALK-positive lung cancer patients previously treated with ALK inhibitors. Journal of Thoracic Oncology. 2015;10(9):S649.	Phase II, open-label, single arm, multicentre study	ALK +ve	≥1 prior ALK inhibitor	Luminespib 70 mg/m2 qw	N/A	ORR (RECIST v1.1) OS PFS] DCR Safety	NR
Case series - ALEC	Metro G, Lunardi G, Bennati C, Chiarini P, Sperduti I, Ricciuti B, et al. Alectinib's activity against CNS metastases from ALK-positive non-small cell lung cancer: a single institution case series. J Neurooncol. 2016;129(2):355-61.	Open label case series	ALK +ve 1 patients from ALEX (crizotinib-naïve) 2 patients from crizotinib experienced non-RCT 8 patients from compassionate use	NR	Alectinib 600 mg bid with a meal (after at least 7 day washout of previous ALK-TKI)	N/A	Activity against CNS metastases	NR
Case series - CER	Schaefer ES, Baik C. Proactive management strategies for potential gastrointestinal adverse reactions with ceritinib in patients with	Open label case series	ALK +ve patients in ceritinib clinical trials	NR	Ceritinib 750 mg qd (fasted)	N/A	Assess proactive GI AE management regimens as approx. 38%	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	advanced ALK-positive non-small-cell lung cancer. Cancer Management and Research. 2016;8:33-8.						of CER pts require dose interruption or reduction for GI AEs	
Cui 2015	Cui S, Zhao Y, Gu A, Ge X, Song Y, Zhang W, et al. Efficacy and tolerability of crizotinib in the treatment of ALK-positive, advanced non-small cell lung cancer in Chinese patients. Medical Oncology. 2015b;32(6).	Open-label, single arm, multicentre study	ALK +ve Chinese patients	Crizotinib - naïve (+/- chemotherapy)	Crizotinib 250 mg bid	N/A	Efficacy Tolerability	NR
LOGK 1401 (UMIN000015094, UMIN000017806)	Iwama E, Goto Y, Murakami H, et al. Alectinib for Patients with ALK Rearrangement–Positive Non–Small Cell Lung Cancer and a Poor Performance Status (Lung Oncology Group in Kyushu 1401). Journal of Thoracic Oncology. 2017; 12(7):1161-6.	Phase II, open-label, single arm, multicentre study	ALK +ve All-comer Poor ECOG PS (2-4)	Any 4 (22.2%) had undergone treatment with crizotinib. 13 (72.2%) were chemotherapy and crizotinib naive.	Alectinib 300mg bid	N/A	ORR PFS ECOG PS Safety PK	9.8 months
Ganetespib phase II 9090-06 (NCT01031225)	Socinski MA, Goldman J, El-Hariry I, Koczywas M, Vukovic V, Horn L, et al. A multicenter phase II study of ganetespib monotherapy in	Phase II, open-label, single arm, multicentre study	4/99 (4%) ALK +ve	≥1 prior therapy The 4 ALK pts were crizotinib-naïve	Ganetspib 200 mg/m2 i.v. qw for 3 wks: 1 wk break	N/A	PFS ORR DCR median PFS Safety OS	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	patients with genotypically defined advanced non-small cell lung cancer. Clinical Cancer Research. 2013;19(11):3068-77.						Molecular markers	
AP26113-11-101 (NCT01449461)	Gettinger S, Bazhenova L, Langer C, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet oncology. 2016; 17(Issue):1683?96.	Phase I/II, open-label, single arm, multicentre study	79/137 (58%) ALK +ve All-comer	Any 90% received prior crizotinib, 47% had ≥2 prior chemotherapy regimens.	Brigatinib 90-180mg qd	N/A	Phase I Recommended Phase II dose Safety MTD PK Phase II ORR PFS TTP OS Safety	15.7 months
X396-CLI-101 (NCT01625234)	Horn L, Infante JR, Reckamp KL, et al. Ensartinib (X-396) in ALK-positive non–small cell lung cancer: Results from a first-in-human phase I/II, multicenter study. Clinical Cancer Research. 2018; 24(12):2771-9.	Phase I/II, open-label, single arm, multicentre study	ALK +ve	Crizotinib 2nd generation ALK TKI	Ensartinib (X396) 25mg orally qd without food then continuously doubled until one patient experienced a drug-related Grade ≥2 AE	N/A	RR Safety PK	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
NP28673 (global) (NCT01801111)	Barlesi F, Dingemans A-M, Yang J-H, et al. Updated efficacy and safety from the global phase II NP28673 study of alectinib in patients (pts) with previously treated ALK+ non-small-cell lung cancer (NSCLC). Annals of oncology Conference: 41st european society for medical oncology congress, ESMO 2016 Denmark	Phase II, open-label, single arm, multicentre study	ALK +ve	Crizotinib (+/- Chemotherapy)	Alectinib 300mg bid	N/A	ORR (IRC) DoR CNS ORR CNS DoR DCR PFS OS Safety	21 months
NP28761 (North America) (NCT01871805)	Camidge DR, Gadgeel S, Ou SH, et al. Updated efficacy and safety data from the phase 2 NP28761 study of alectinib in ALK-positive non-small-cell lung cancer. Journal of Thoracic Oncology. 2017; 12(1):S378.	Phase II, open-label, single arm, multicentre study	ALK +ve	Crizotinib (+/- Chemotherapy)	Alectinib 300 mg bid	N/A	ORR (IRC by RECIST v1.1) Inv ORR PFS OS CNS ORR DCR Safety	17.0 months
PROFILE 1005 (NCT00932451)	Riely GJ, Kim DW, Crinò L, Janne PA, Blackhall FH, Camidge DR, et al. Phase 2 data for crizotinib (PF-02341066) in ALK-positive advanced non-small cell lung cancer (NSCLC): Profile 1005.	Phase II, open-label, single arm, multicentre study	ALK +ve	Crizotinib-naïve Chemotherapy	Crizotinib 250 mg bid	N/A	NR	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Journal of Thoracic Oncology. 2011;6(6):S411-S2.							
Kawano 2013 (UMIN000002847)	Kawano Y, Ohyanagi F, Yanagitani N, Kudo K, Horiike A, Tanimoto A, et al. Pemetrexed and cisplatin for advanced non-squamous non-small cell lung cancer in Japanese patients: Phase ii study. Anticancer Research. 2013;33(8):3327-34.	Phase II, open-label, non-RCT, multicentre study	6/39 analysed (15.4%) ALK+ve Japanese pts	Treatment-naïve	Pemetrexed 500mg/m2 D1 followed by cisplatin 75mg/m2 D1 3-wk cycle; Max 4 cycles	N/A	ORR Toxicity PFS OS	19.0 months
IPI-504-03 (NCT00431015)	Sequist LV, Natale RB, Senzer NN, Martins R, Lilenbaum R, Gray JE, et al. Association between anaplastic lymphoma kinase rearrangements (rALK) and the clinical activity of IPI-504 (retaspimycin hydrochloride), a novel Hsp90 inhibitor, in patients with non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2010b;28(15).	Phase II, open-label, non-RCT	15/76 (19.7%) ALK +ve	≥1 TKI	Retaspimycin hydrochloride (IPI-504)	NR	ORR PFS Safety	NR
ALTA (NCT02094573)	Kim D, Tiseo M, Ahn M, et al. Brigatinib in Patients With	Phase II, open-label, RCT,	ALK +ve	Crizotinib (+/- Chemotherapy)	Brigatinib 90 mg qd for 7 days	Brigatinib 180 mg qd for 7 days	Inv ORR Inv PFS	8.0 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: a Randomized, Multicenter Phase II Trial. Journal of Clinical Oncology. 2017; 35(Issue):2490?8.	multicentre study					IRC Intracranial ORR Safety	
CALGB 30406 (NCT00126581)	Stinchcombe T, Sholl LM, Wang XF, Gu L, Socinski MA, Rodig SJ, et al. An analysis of the prevalence of HER2 and KRAS mutations, and ALK rearrangements and clinical outcomes in Cancer and Leukemia Group B [CALGB (Alliance)] trial 30406 in advanced non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2013;31(15).	Phase II, open-label, RCT, multicentre study	8/114 (7%) ALK +ve	Treatment-naïve	Erlotinib qd orally D1-21 continuously	Erlotinib + carboplatin i.v. + paclitaxel i.v. D1 of each 21 day cycle (max 6 cycles)	ORR PFS OS Safety	NR
EURTAC (NCT00446225)	Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a	Phase III, open-label, RCT, multicentre study	EGFR +ve and ALK +ve in 15.79% (15/95 who had tumour specimen available)	Treatment-naïve for metastatic disease Neo-adjuvant or adjuvant chemotherapy was allowed if it ended ≥6	Erlotinib 150mg qd orally	Cisplatin 75 mg/sqm D1 + docetaxel 75 mg/sqm D1 or gemcitabine 1250 mg/sqm D1&8 Where	PFS (ITT population) Response rate OS EGFR mutation analysis in serum Safety	18.9 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012; 13(3):239-46			months before entry to study		patient could not have cisplatin: carboplatin AUC 6 + docetaxel 75 mg/sqm, or carboplatin AUC 5 + gemcitabine 1000 mg/sqm		
JP28927 (JapicCTI-132186)	Hida T, Nakagawa K, Seto T, et al. Pharmacologic study (JP28927) of alectinib in Japanese patients with ALK+ non-small-cell lung cancer with or without prior crizotinib therapy. Cancer Science. 2016; 107(Issue):1642?6.	Open-label, RCT, multicentre study	ALK +ve All-comer	Any 29 (82.9%) had received at least one prior ALK inhibitor. 28 patients had received previous crizotinib treatment, 23 were defined as crizotinib failures.	Alectinib 300 mg bid (using 150 mg capsules)	Alectinib 300 mg bid (using 20/40 mg capsules)	Bioequivalence and effect of food on the bioavailability of 150 mg and 20/40 mg capsules of alectinib under fasting conditions	NR
Lee 2016 (NCT01712217)	Lee JS, Han JY, Ahn MJ, Oh IJ, Kim HR, Lee DH, et al. Addition of HSP90 inhibitor onalespib to crizotinib prior to progression in patients with ALK-pos NSCLC: Results of a randomized phase 2	Phase I/II, open-label, RCT, multicentre study	ALK +ve	Crizotinib	Crizotinib 250mg bid	Crizotinib 250mg bid + onalespib 220 mg/m2 D1,8,and 15 Q28 D	PFS OS ORR Safety	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	study. Journal of Clinical Oncology. 2016;34.							
Zhao 2015	Zhao J, Zhang K, Zhang L, Wang H. [Clinical Efficacy of Crizotinib in Advanced ALK Positive Non-small Cell Lung Cancer]. Zhongguo fei ai za zhi = Chinese journal of lung cancer [Internet]. 2015; 18(10):[616-20 pp.].	Phase III/IV, open-label, RCT, multicentre study	ALK +ve	1-2 lines previous standard treatments.	Crizotinib 250 mg bid	Docetaxel 75mg/m2 q3w	RR PFS	NR
Zhang 2013	Zhang L, Huang Y, Hu Z, Liu YP, Zhou J, Xu N, et al. Biomarker analysis of a randomized, controlled, multicenter clinical trial comparing pemetrexed/cisplatin and gmcitabine/ cisplatin as first-line treatment for advanced nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology. 2013;8:S330.	RCT	12% ALK+ (29/233)	Treatment-naïve	Cisplatin + pemetrexed q3w, 6 cycles (dose NR)	Cisplatin + gemcitabine q3w, 6 cycles (dose NR)	PFS Biomarkers predicting of 1L efficacy	NR

Table 24: Summary study characteristics for the 25 studies that met the inclusion criteria for the update ALK+ SLR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
ALEX (NCT02075840, 2013-004133-33, EudraCT Number)	Peters S, Camidge D, Shaw A, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2017; 377:829-38.	Phase III, open-label, RCT, multicentre study	ALK +ve	Treatment-naïve	Alectinib 300 mg bid taken with food	Crizotinib 25mg bid taken with or without food	PFS CNS progression OS ORR DoR Safety	18.6 months (alectinib) 17.6 months (crizotinib)
ALTA-1L (NCT02737501)	Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018.	Phase III, open-label, RCT, multicentre study	ALK +ve	≤1 prior systemic anticancer therapy ALK inhibitor-naïve	Brigatinib 180mg qd after a 7-day lead-in period of 90mg qd	Crizotinib 250mg bid	PFS (BICR) ORR Intracranial ORR Safety	11.0 months (brigatinib) 9.3 months (crizotinib)
ALUR (NCT02604342)	Novello S, Mazieres J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann	Phase III, open-label, RCT, multicentre study	ALK +ve	2 prior lines of systemic therapy, including 1 line of platinum-based doublet chemotherapy Crizotinib	Alectinib 600mg bid	Pemetrexed 500 mg/m2 every 3 weeks or docetaxel 75 mg/m2 every 3 weeks	Inv PFS CNS ORR PFS (BIRC) ORR DCR Inv DoR DoR (BICR) CND DCR OS Safety	6.5 months (alectinib) 5.8 months (chemotherapy)

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Oncol. 2018; 29(6):1409-16.							
ASCEND-4 (NCT01828099)	Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): A randomised, open-label, phase 3 study. The Lancet. 2017.	Phase III, open-label, RCT, multicentre study	ALK +ve	Untreated with any systemic anticancer therapy (except neoadjuvant or adjuvant systemic therapy [if relapse had occurred >12 months from the end of therapy]	Ceritinib 750mg qd orally	Cisplatin 75 mg/sqm every 3 weeks for 4 cycles or Carboplatin AUC 5-6 + pemetrexed 500 mg/sqm every 3 weeks for 4 cycles followed by pemetrexed maintenance	PFS IRC-assessed by RECIST v1.1 (FAS) OS Inv PFS ORR DoR DCR time to response Intracranial ORR Intracranial DCR Intracranial DOR Intracranial CBR PROs Safety PK	NR
ASCEND-5 (NCT01828112)	Shaw A, Kim T, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously	Phase III, open-label, RCT, multicentre study	ALK +ve	Crizotonib and 1-2 lines of chemotherapy	Ceritinib 750mg qd	Pemetrexed 500 mg/m2 every 3 weeks or docetaxel 75 mg/m2 every 3 weeks	PFS (BICR) ORR (BICR) DCR (BICR) Inv PFS Inv ORR Inv DOR OS	16.5 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. The lancet Oncology. 2017; 18:874-86.						Safety PROs	
J-ALEX (JapicCTI-132316)	Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet (London, England). 2017; 390:29-39.	Phase III, open-label, RCT, multicentre study	ALK +ve	ALK TKI naïve, chemotherapy naïve or 1 previous line of chemotherapy (64% treatment-naïve, 36% 1 previous chemotherapy)	Alectinib 300 mg bid orally	Crizotinib 250 mg bid orally	PFS (BIRC) Inv PFS OS ORR DoR TTR PROs Safety PK	12.0 months (alectinib) 12.2 months (crizotinib)
PROFILE 1007 (NCT00932893)	Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. New England Journal of Medicine.	Phase III, open-label, RCT, multicentre study	ALK +ve	1 prior platinum-based chemotherapy regimen, crizotinib-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 or Docetaxel 75 mg/m2	PFS (BIRC) OS ORR DoR TTR Safety PROs	12.2 months for OS

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	2013;368(25):2385-94.							
PROFILE 1014 (NCT01154140)	Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine [Internet]. 2014; 371(23):[2167-77 pp.]	Phase III, open-label, RCT, multicentre study (crossover permitted following progression)	ALK +ve	Treatment-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 or carboplatin AUC 5-6mg/mL/min 3 wk cycle Max 6 cycles	PFS (BICR) ORR OS DoR TTR OS Safety PROs	17 months
PROFILE 1029, A8081029 (NCT01639001)	Wu YL, Lu S, Lu Y, et al. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018; 13(10):1539-48.	Phase III, open-label, RCT, multicentre study (crossover permitted following progression)	ALK +ve	Treatment-naïve	Crizotinib 250 mg bid	Pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 or carboplatin AUC 5-6mg/mL/min 3 wk cycle Max 6 cycles	PFS (BICR) ORR OS TTP Safety PROs	22.5 months (crizotinib) 21.6 months (chemotherapy) for OS
LOGK 1401 (UMIN000015094, UMIN000017806)	Iwama E, Goto Y, Murakami H, et al. Alectinib for Patients with ALK	Phase II, open-label, single arm,	ALK +ve All-comer Poor ECOG PS (2-4)	Any 4 (22.2%) had undergone	Alectinib 300mg bid	N/A	ORR PFS ECOG PS	9.8 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Rearrangement–Positive Non–Small Cell Lung Cancer and a Poor Performance Status (Lung Oncology Group in Kyushu 1401). Journal of Thoracic Oncology. 2017; 12(7):1161-6.	multicentre study		treatment with crizotinib. 13 (72.2%) were chemotherapy and crizotinib naive.			Safety PK	
AF-001JP (JapicCTI-101264)	Tamura T, Kiura K, Seto T, et al. Three-year follow-up of an alectinib phase I/II study in ALK-positive non-small-cell lung cancer: aF-001JP. Journal of Clinical Oncology. 2017; 35(Issue):1515-21	Phase I/II, open-label, single arm, multicentre study	ALK +ve Japanese patients	≥1 prior chemotherapy regimens, crizotinib-naïve	Alectinib 300mg bid	N/A	ORR (IRC) DCR PFS OS PK Safety	3 years
ALTA (NCT02094573)	Kim D, Tiseo M, Ahn M, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: a Randomized, Multicenter Phase II Trial. Journal of	Phase II, open-label, RCT, multicentre study	ALK +ve	Crizotinib (+/- Chemotherapy)	Brigatinib 90 mg qd for 7 days	Brigatinib 180 mg qd for 7 days	Inv ORR Inv PFS IRC Intracranial ORR Safety	8.0 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Clinical Oncology. 2017; 35(Issue):2490?8.							
ASCEND-3 (NCT01685138)	Felip E, Orlov S, Park K, et al. Phase 2 study of ceritinib in ALKi-naive patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC): whole body responses in the overall pt group and in pts with baseline brain metastases (BM). Annals of oncology Conference: 41st european society for medical oncology congress, ESMO 2016 Denmark	Phase II, open-label, single arm, multicentre study	ALK +ve	≤3 lines prior chemotherapy ALK inhibitor-naïve	Ceritinib 750 mg qd	N/A	ORR (INV) DOR DCR TTR ORR (BIRC), Safety PFS (BIRC or INV) OS Intracranial ORR	23.4 months
ASCEND-9 (NCT02450903)	Hida T, Seto T, Horinouchi H, et al. Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma kinase-rearranged metastatic non-small-cell lung	Phase II, open-label, single arm, multicentre study	ALK +ve Japanese patients	Alectinib ≤1 chemotherpy regimen	Ceritinib 750 qd orally (given in a fasted state).	N/A	ORR DCR TTR DoR PFS OS Intracranial ORR Safety	11.6 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	cancer in Japan: ASCEND-9. Cancer Science. 2018; 109(9):2863-72.							
ATLANTIC (NCT02087423)	Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol. 2018; 19(4):521-36.	Phase II, open-label, single arm, multicentre study	Advanced NSCLC, PD-L1 expression in at least 25% of tumour cells	≥2 previous systemic regimens, including platinum-based chemotherapy (and tyrosine kinase inhibitor therapy if indicated); EGFR+ ve patients must have received an EGFR TKI ALK+ ve patients must have received an ALK TKI, before or after the platinum-based chemotherapy regimen.	Durvalumab	N/A	ORR OS PFS DR DCR TTR Safety	Cohort 1: 6.7 months Cohort 2: 10.3 months
CHECKMATE 370 (NCT02574078)	Spigel DR, Reynolds C, Waterhouse D, et al. Phase 1/2 Study of the Safety and Tolerability of	Phase I/II, open-label, 5 cohort, mulitcentre study	ALK +ve Untreated or active CNS metastases	Cohort E: Treatment naive	Cohort E: Nivolumab 240 mg IV over 30 minutes every 2	N/A	Safety ORR	7.2 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation — Positive Advanced Non–Small Cell Lung Cancer (CheckMate 370). Journal of Thoracic Oncology. 2018; 13(5):682-8.				weeks + crizotinib 250 mg orally bid			
JP28927 (JapicCTI-132186)	Hida T, Nakagawa K, Seto T, et al. Pharmacologic study (JP28927) of alectinib in Japanese patients with ALK+ non-small-cell lung cancer with or without prior crizotinib therapy. Cancer Science. 2016; 107(Issue):1642?6.	Open-label, RCT, multicentre study	ALK +ve All-comer	Any 29 (82.9%) had received at least one prior ALK inhibitor. 28 patients had received previous crizotinib treatment, 23 were defined as crizotinib failures.	Alectinib 300 mg bid (using 150 mg capsules)	Alectinib 300 mg bid (using 20/40 mg capsules)	Bioequivalence and effect of food on the bioavailability of 150 mg and 20/40 mg capsules of alectinib under fasting conditions	NR
CAUY922A220 (NCT01124864)	Felip E, Barlesi F, Besse B, et al. Phase 2 Study of the HSP-90 Inhibitor AUY922 in Previously Treated and Molecularly	Phase II, open-label, single arm, multicentre study	22/121 (18%) ALK +ve,	≥2 prior lines of therapy	Luminespib 70 mg/m2 qw	N/A	Inv ORR OS PFS Safety	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	Defined Patients with Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018; 13(4):576-84.							
AP26113-11-101 (NCT01449461)	Gettinger S, Bazhenova L, Langer C, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet oncology. 2016; 17(Issue):1683?96.	Phase I/II, open-label, single arm, multicentre study	79/137 (58%) ALK +ve All-comer	Any 90% received prior crizotinib, 47% had ≥2 prior chemotherapy regimens.	Brigatinib 90-180mg qd	N/A	Phase I Recommended Phase II dose Safety MTD PK Phase II ORR PFS TTP OS Safety	15.7 months
X396-CLI-101 (NCT01625234)	Horn L, Infante JR, Reckamp KL, et al. Ensartinib (X-396) in ALK-positive non–small cell lung cancer: Results from a first-in-human phase I/II, multicenter study. Clinical Cancer Research. 2018; 24(12):2771-9.	Phase I/II, open-label, single arm, multicentre study	ALK +ve	Crizotinib and/or 2nd generation ALK TKI	Ensartinib (X396) 25mg orally qd without food then continuously doubled until one patient experienced a drug-related Grade ≥2 AE	N/A	RR Safety PK	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
NCT01625234 and NCT02767804	Reckamp KL, Wakelee HA, Patel S, et al. CNS activity of ensartinib in ALK1 non-small cell lung cancer (NSCLC) patients (pts). Annals of Oncology. 2017; 28:iii31-2.	Phase I/II, multicentre study	ALK +ve with asymptomatic CNS metastases (with or without systemic disease)	ALK TKI naïve, prior crizotinib or 2nd generation ALK TKI	Ensartinib on continuous 28-day schedule	N/A	RR Intracranial RR DCR DoR	NR
NCT01970865	Felip-Font E, Shaw AT, Solomon BJ, et al. Efficacy and safety of lorlatinib in patients (pts) with ALK1 non-small cell lung cancer (NSCLC) previously treated with 2nd-generation ALK TKIs. Annals of Oncology. 2017; 28:v478-9.	Phase II, multicentre study	ALK +ve	≥1 2nd-Generation ALK TKIs	Lorlatinib 100mg qd	N/A	ORR Intracranial ORR	NR
NP28673 (global) (NCT01801111)	Barlesi F, Dingemans A-M, Yang J-H, et al. Updated efficacy and safety from the global phase II NP28673 study of alectinib in patients (pts) with previously treated ALK+ non-small-	Phase II, open-label, single arm, multicentre study	ALK +ve	Crizotinib (+/- Chemotherapy)	Alectinib 300mg bid	N/A	ORR (IRC) DoR CNS ORR CNS DoR DCR PFS OS Safety	21 months

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
	cell lung cancer (NSCLC). Annals of oncology Conference: 41st european society for medical oncology congress, ESMO 2016 Denmark							
NP28761 (North America) (NCT01871805)	Camidge DR, Gadgeel S, Ou SH, et al. Updated efficacy and safety data from the phase 2 NP28761 study of alectinib in ALK-positive non-small-cell lung cancer. Journal of Thoracic Oncology. 2017; 12(1):S378.	Phase II, open-label, single arm, multicentre study	ALK +ve	Crizotinib (+/- Chemotherapy)	Alectinib 300 mg bid	N/A	ORR (IRC by RECIST v1.1) Inv ORR PFS OS CNS ORR DCR Safety	17.0 months
US Expanded Access Program (EAP)	Patel JD, Gadgeel SM, Ou SI, et al. Alectinib following prior ALK tyrosine kinase inhibitor (TKI) therapy: Results from the US expanded access program (EAP). Journal of Thoracic Oncology. 2017; 12(11):S1573.	Real world study	ALK +ve	ALK TKI therapy	Alectinib 600mg bid	N/A	ORR DCR Safety	NR

Study name (NCT number)	Primary reference	Study design	Population	Prior treatment	Intervention	Comparator	Key endpoints	Median follow-up
Wakelee, 2017	Wakelee H, Sanborn R, Nieva J, et al. Response to ensartinib in TKI naïve ALK+ NSCLC patients. Journal of Thoracic Oncology. 2017; 12(11):S1826.	Real world study	ALK +ve	ALK TKI treatment naïve Prior chemotherapy	Ensartinib 225 mg qd on a continuous 28-day schedule	N/A	PFS ORR Safety	N/R

A12. Please provide reasons for the studies excluded from the ROS1+ SLR, original and update ALK+ SLR and all studies listed as included from the SLRs that were not carried forward for the MAIC. Specifically:

a) please explain why only 11 prospective and 9 retrospective studies were considered for the MAIC (page 60 Appendix D) out of the 70 identified (A11).

All studies identified that investigated treatments of relevance to the UK setting were considered for the MAIC. Those not considered were those investigating treatments not of relevance to the UK setting but that were included as interventions of interest in the SLR given their global coverage.

b) please provide a table summarising your feasibility assessment of the 11 & 9 studies including reasons for exclusion from the MAIC.

The requested table is provided as Table 25.

Table 25: Feasibility assessment of studies including reasons for exclusion from the MAIC

Study name (study number)	Patient population	Intervention	Comparator	Included in MAIC	Reason for exclusion
Prospective studies					
PROFILE 1001 (NCT00585195)	ROS1 +ve	Crizotinib	N/A	Yes	N/A
OX-ONC (NCT01945021)	ROS1 +ve	Crizotinib	N/A	No	• 39.4% of patients were at 3L or 4L, which meant that MAIC of entrectinib vs crizotinib would represent the relative effect of treatment in patients treated at 2L-4L line. • The outcome reporting was incomplete, as there was no KM curve for OS available, which meant this couldn't be included in the analysis. • OX-CNC included exclusively east Asian patients treated in China, Japan, South Korea and Taiwan. Therefore, the MAIC would represent the relative treatment effect observed in an east Asian population.
ALEX (NCT02075840)	ALK +ve	Alectinib	Crizotinib	No	• An MAIC of entrectinib vs crizotinib based the crizotinib arm of the ALEX study would lead to a result that represents ALK-positive patients. • The objective of the MAIC was to compare the relative effects of entrectinib versus alternative treatments in ROS1 +ve NSCLC patients. • The PROFILE 1001 study provides evidence of the effect of crizotinib in the appropriate ROS1 +ve population this study was the preferred evidence source for this comparison.
J-ALEX (JapicCTI-132316)	ALK +ve	Alectinib	Crizotinib	No	• An MAIC of entrectinib vs crizotinib based the crizotinib arm of the J-ALEX study would lead to a result that represents ALK-positive patients. • The objective of the MAIC was to compare the relative effects of entrectinib versus alternative treatments in ROS1 +ve NSCLC patients.

					• The PROFILE 1001 study provides evidence of the effect of crizotinib in the appropriate ROS1 +ve population this study was the preferred evidence source for this comparison.
ALTA-1L (NCT02737501)	ALK +ve	Brigatinib	Crizotinib	No	• An MAIC of entrectinib vs crizotinib based the crizotinib arm of the ALTA-1L study would lead to a result that represents ALK-positive patients. • The objective of the MAIC was to compare the relative effects of entrectinib versus alternative treatments in ROS1 +ve NSCLC patients. • The PROFILE 1001 study provides evidence of the effect of crizotinib in the appropriate ROS1 +ve population this study was the preferred evidence source for this comparison.
ASCEND-4	ALK +ve	Ceritinib	Pemetrexed + cisplatin/carboplatin followed by pemetrexed maintenance	Yes	N/A
PROFILE 1014	ALK +ve	Crizotinib	Pemetrexed + cisplatin/carboplatin	No	• PROFILE 1014 compared crizotinib 250mg twice daily with pemetrexed 500mg/m2 daily, platinum-based chemotherapy (either cisplatin 75mg/m2 or carboplatin AUC 5-6) as first line treatment in patients with ALK-positive NSCLC. • PROFILE 1014 did not include pemetrexed maintenance. Whereas, patients treated with pemetrexed plus platinum in UK clinical practice would be expected to go on to receive pemetrexed maintenance in the absence of disease progression. • The ASCEND-4 study provides this evidence, as such this is preferred evidence source for this comparison.
PROFILE 1029	ALK +ve	Crizotinib	Pemetrexed + cisplatin/carboplatin	No	• PROFILE 1029 compared crizotinib 250mg twice daily with pemetrexed 500mg/m2 daily, platinum-based chemotherapy (either cisplatin 75mg/m2 or carboplatin AUC 5-6) as first line treatment in patients with ALK-positive NSCLC. • PROFILE 1029 included only East Asian patients • PROFILE 1029 did not include pemetrexed maintenance. Patients treated with pemetrexed plus platinum in UK clinical

					practice would be expected to go on to receive pemetrexed maintenance in the absence of disease progression. • The ASCEND-4 study provides this evidence, as such this is preferred evidence source for this comparison.
PROFILE 1007	ALK +ve	Crizotinib	Pemetrexed or docetaxel	Yes	N/A
ALUR	ALK +ve	Alectinib	Pemetrexed or docetaxel	No	• ALUR compared the effects in ALK-positive NSCLC patients of alectinib 600mg twice daily versus either pemetrexed (500mg/m2) or docetaxel (75mg/m2) every 3 weeks. • The comparison of interest in this context is entrectinib versus chemotherapy in patients who had received one prior line of therapy. • Both PROFILE 1007 and ALUR included a chemotherapy arm where patients could receive one of either docetaxel monotherapy or pemetrexed monotherapy as second-line treatment. • The sample size in the ALUR study was 35 patients compared to 174 in PROFILE 1007. • The median follow-up in the ALUR study was much shorter at approximately 6 months compared to approximately 12 months in PROFILE 1007. Longer follow-up data are considered preferable for analysis. • Based on the assessment of patient characteristics, PROFILE 1007 is more similar to the population in the entrectinib integrated analysis. • Therefore, data from PROFILE 1007 is recommended for the chemotherapy comparison for the second-line chemotherapy setting.
ASCEND-5	ALK +ve	Ceritinib	Pemetrexed or docetaxel	No	• The ASCEND-5 study compared ceritinib with physician's choice of either pemetrexed (500mg/m2) or docetaxel (75mg/m2) every 21 days. However, this study included both patients who had received one prior line of therapy and patients who had received two prior lines of therapy.

					• The comparison of interest in this context is entrectinib versus chemotherapy in patients who had received one prior line of chemotherapy. • PROFILE 1007 included only patients who had received one prior line of therapy which was considered more relevant to the decision problem.
Retrospective studies					
METROS trial (NCT02499614)	ROS +ve	Crizotinib	N/A	No	• Study presentation limited to conference abstracts that did not report sufficient information for MAIC analysis.
ACSe trial (NCT02034981)	ROS +ve	Crizotinib	N/A	No	• No patients were reported to have received crizotinib as first-line treatment, which meant that MAIC of entrectinib vs crizotinib would represent the relative effect of treatment in patients treated at 2L or later. • The most common treatment line for crizotinib use was 4L or beyond (41.0% of patients) • OS data for which a KM curve was available were immature; PFS data inconsistencies across reports
EUROS1	ROS1 +ve	Crizotinib	N/A	No	• A single patient received crizotinib as first-line treatment, which meant that MAIC of entrectinib vs crizotinib would represent the relative effect of treatment in patients treated at 2L or later. • The most common treatment line for crizotinib use was 5L or beyond (41.9% of patients) • OS data not reported
Bennati 2015	ROS1 +ve	Crizotinib	N/A	No	• Study presentation limited to conference abstracts that did not report sufficient information for MAIC analysis.
Zhang 2016	ROS1 +ve	Crizotinib	N/A	No	• Details of treatment(s) received was not clearly reported. • There were 15 patients who had received crizotinib • Treatment effects for individual treatments at each line was not reported (and could not be inferred) • OS data not reported
Scheffler 2015	ROS1 +ve	Crizotinib	N/A	No	• Details of treatment(s) received was not clearly reported.

					• Among the 14 patients with Stage IV disease, only five received crizotinib treatment. • Treatment effects for individual treatments at each line was not reported (and could not be inferred) • OS data immature; PFS data not reported
Patil 2018	ROS1 +ve	Crizotinib	N/A	No	• Details of treatment(s) received was not clearly reported. • Outcome reporting was limited to PFS and CNS progression in a group of patients with CNS metastasis • OS data not reported
Chen 2016	ROS1 +ve	Pemetrexed	Pemetrexed + Platinum	No	• Small sample size (n=19) • Patients had received a complex mixture of different treatments across multiple treatment lines and treatment effects for individual treatments at each line was not reported (and could not be inferred) • Younger patient population than the entrectinib integrated analyses (43.8 vs 53 years)
Zhang 2018	ROS1 +ve	Pemetrexed-containing	Non-pemetrexed-containing	No	• Study presentation limited to conference abstracts that did not report sufficient information for MAIC analysis.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness

B1. Priority: Please use the latest KM data available for entrectinib (30 October 2018 CCOD) for the ERG's preferred efficacy set (defined in A3) to fit OS, PFS and TTD curves for entrectinib, following the NICE DSU TSD 14 guidance, as currently done in the CS and model. Following that please:

a) **Include the KM data in the model as currently done in the "KM OS", "KM PFS" and "KM ToT" tabs of the model;**

b) **Use the TTD curve to estimate treatment costs for entrectinib (with different distributions available as model inputs);**

c) **Use the fitted OS and PFS curves to estimate progression and survival for entrectinib in the economic analysis (with different distributions available as model inputs).**

The latest trial data cut-off for progression-free survival, time on treatment and overall survival for the ERG's preferred efficacy set has been added to the economic model. This data is from the 31st October 2018 clinical cut-off date.

The updated model is provided alongside this response document.

B2. Priority: Please provide KM data in Excel format (with numbers at risk) for the latest OS and PFS data available for crizotinib from PROFILE 1001 (Shaw 2019 - reference 48) used to run the MAIC requested in A6.

Please find KM data requested in Appendix C.

B3. Priority: Similar to Figure 6 and Figure 7 in the CS, please compare the unadjusted crizotinib OS and PFS data requested in B2 with the MAIC-adjusted KM OS and PFS crizotinib data used to run the MAIC requested in A6.

We presume this should read "please compare the unadjusted **entrectinib** OS and PFS data requested in B2 with the MAIC-adjusted KM OS and PFS **entrectinib** data used to run the MAIC requested in A6" as it was entrectinib data that were adjusted.

Please see Figure 1, Figure 2 and Figure 3 of the response to Question A6 for this comparison.

B4. Priority: The CS reports that ToT data from ALKA; STARTRK-1; and STARTRK-2 were used to estimate the cost of treatment with entrectinib, however the ERG could not find these data in the respective studies' CSRs. Please provide the following:

a) **The definition used for the ToT data analysis in the studies and clarify if the analysis censored deaths;**

ToT was defined as duration of therapy with entrectinib, calculated as:

(Last dose day - First dose day + 1)/30.4375

For patients still on therapy at the data cut-off date the last dose day was set at the clinical cut-off date. Only patients who had completed therapy per the CRF page were considered as having a treatment discontinuation event. All others were censored at this last known dose date/CCOD. Death was not censored.

b) **Further details on the safety population used to estimate ToT, and how it differs from the population used to estimate PFS and OS outcomes with regard to treatment dose received (and any other relevant aspects);**

ToT analysis was performed on the same efficacy set used to estimate PFS and OS.

c) **Please specify if all patients included in the ToT analysis were ROS1+ NSCLC patients; if they all received 600mg entrectinib; and if STARTRK-2 patients were selected based on the >12 months follow-up from response criteria.**

All patients included in the ToT analysis were ROS1+ NSCLC patients as this was performed on the same efficacy set used for PFS & OS.

Updated ToT incorporated into the updated model to be provided will be based on the ERG's preferred efficacy set and will thus include ROS1 NSCLC patients who received 600ng entrectinib in STARTRK-2 (irrespective of follow-up).

B5. Priority: Please provide the raw patient-level data underlying Figure 4 and Figure 5 (page 38 of reference 43 in the CS reference pack) in Excel format. Please provide the data by patient identified by trial, as currently shown in Figure 4 and Figure 5.

Unfortunately, due to legal and governance reasons, Roche is not able to provide raw patient-level data. However, if still relevant in light of the response provided to question B7 and where feasible, Roche may be able to conduct further prospective analyses requested by the ERG

B6. Priority: Based on the integrated PFS and TTD data used in the company's base case analysis and provided in the company's model (shown below), the majority of patients discontinued treatment before progression. However, Figure 4 and Figure 5 (page 38 of reference 43 in the CS reference pack) suggest that only 1 patient in the integrated dataset discontinued treatment before progression. Please explain this discrepancy.

Figure 8 Entrectinib ToT and PFS KM data

Source: Company's model

We are unsure on how the ERG are interpreting these figures as Figure 4 and Figure 5 do not show that only 1 patient in the integrated dataset discontinued treatment before progression. As provided in Appendix D.2, seven patients in the primary efficacy set discontinued treatment for reasons other than progressive disease. Many patients are censored in PFS and ToT outcomes.

B7. Priority: Please provide the patient-level data in Figure 4 and Figure 5 (page 38 of reference 43 in the CS reference pack) for the ERG's preferred efficacy set and also provide the same comparative analysis (as requested in B6) for the ToT and PFS data for patients in the ERG's preferred efficacy set (as requested in B1a).

A comparative analysis for patients in the ERG's preferred efficacy set as of the CCOD 30 October 2018 is provided in Table 26. As can be seen from these data, of those who have had both events, [redacted] patients had a shorter ToT than PFS, [redacted] patients had a longer ToT than PFS and [redacted] patients had an equivalent ToT and PFS (rounding to one decimal place on a month time scale).

The differences between ToT and PFS can be attributed in part to the different methods of patient assessment in the context of potential discontinuation. PFS is based on blinded independent central review (BICR) whereas ToT is based on investigator assessment (IA). Therefore, a patient may be discontinued from study treatment at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue on study. In contrast, PFS is defined as the time from the first dose of entrectinib to first documentation of radiographic disease progression or death due to any cause (whichever occurs first), based on the results of the BICR.

Table 26: ToT and PFS data - ERG's preferred efficacy set - CCOD 30 Oct 2018

TTD_STATUS	PFS_STATUS	COMPARISON	N
Censored	Censored	ToT < PFS	[redacted]
Censored	Censored	ToT = PFS	[redacted]
Censored	Censored	ToT > PFS	[redacted]

Censored	Event	ToT = PFS	[redacted]
Censored	Event	ToT > PFS	[redacted]
Event	Censored	ToT < PFS	[redacted]
Event	Censored	ToT = PFS	[redacted]
Event	Censored	ToT > PFS	[redacted]
Event	Event	ToT < PFS	[redacted]
Event	Event	ToT = PFS	[redacted]
Event	Event	ToT > PFS	[redacted]
Key: CCOD, clinical cut-off date; PFS, progression-free survival; ToT, time on treatment			

B8. Priority: The CS (page 114) refers to the RFPSTM-adjusted HR from the latest data cut from PROFILE 1014 (HR = 0.346) as the accepted measure of relative treatment effectiveness in TA529. However, the ERG could not find the mentioned HR reported in the TA529 documents, or confirmation that the latter was accepted by the committee. Therefore, can the company please point the ERG to the relevant TA529 documents reporting the referred HR and the documents discussing the appropriateness of using this estimate.

The hazard ratio (HR) used in the model (HR = 0.346) is taken from the latest data reported from PROFILE 1014 which is presented in a publication by Solomon et al[1] (this was provided as reference 65 in the Document B reference pack). Data were redacted in the company submission for TA529 but it was noted that a later data cut than that used in TA406 was used. Our assumption is that this later data cut is that reported in the Solomon et al. publication, and our apologies that this was not made clear in the company submission.

Within TA529, the company submitted two analyses for the comparison to pemetrexed plus platinum; one analysis where independent curve fits to ALK-positive NSCLC for crizotinib and pemetrexed plus platinum therapy from TA406 were used as a proxy for ROS1-positive NSCLC and one analysis where the HR from PROFILE 1014 was applied to the parametric curves fitted to PROFILE 1001. Both analyses were considered by the committee as part of this appraisal.

B9. Priority: Please explain why the OS and PFS KM data used in the economic model is based on 51 patients (and not 53 as per the population in the integrated analysis).

The OS and PFS KM data used in the economic model is based on [redacted] patients (and not [redacted]). Unfortunately, there was a mistake in the number at risk shown at time 0 in the original model submitted. 2 patients censored at day 1 were excluded from the OS and PFS KM data and therefore the number of patients should have been [redacted] and not [redacted]. The KM survival estimates and number at risk were correct at all other time points with no changes to the model results. The corrected PFS and OS KM data is presented below in Table 27 and Table 28.

Table 27: Updated PFS KM data

strata	time_months	surv	lower	upper	n.risk	n.cum.events
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

strata	time_months	surv	lower	upper	n.risk	n.cum.events
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Updated OS KM data

strata	time_months	surv	lower	upper	n.risk	n.cum.events
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B10. Priority: Please justify the choice of 24 months for the cut-off point of entrectinib's treatment effect in the company's scenario analysis.

The 24-month cut-off point of entrectinib's treatment effect is an arbitrary time point selected as post that point, the progression-free survival hazard is stabilized for both entrectinib and crizotinib and censoring becomes high. Therefore, 24 months is a robust timeframe of the observed data.

B11. Priority: The CSR for STARTRK-2 specifies data collection on subsequent treatments received by study patients. Please provide data on subsequent treatments received by patients (please specify the proportion of patients receiving each treatment; type of treatment received; and treatment duration)

for the patients included in the integrated analysis used in the company's MAIC.

Available subsequent therapy data is provided in Figure 9, which reports the proportion of patients in STARTRK-1 and STARTRK-2 who received subsequent therapy after entrectinib, and the specific treatment received. Further data requested are not available.

Figure 9: Subsequent treatments received by patients in STARTRK-1 and STARTRK-2

Anti-Cancer Treatments Administered After Progression, ROS1 NSCLC Efficacy Evaluable enrolled up to APR 30, 2017
Protocols: GO40782, GO40783, GO40784
CCOD: May 31 2018, DBL: Jul 31 2018

WHO ATC Level 2 (Therapeutic Class) Generic Term	ST01 (N=7)	ST02 (N=37)	Total (N=53)
Patients with Anti-Cancer Treatment Administered After Progression by BICR RECIST Assessment	2 (28.6%)	12 (32.4%)	14 (26.4%)
ANTINEOPLASTIC AGENTS			
Patients with Anti-Cancer Treatment Administered After Progression by BICR RECIST Assessment	0	12 (32.4%)	12 (22.6%)
PEMETREXED	0	8 (21.6%)	8 (15.1%)
CARBOPLATIN	0	6 (16.2%)	6 (11.3%)
CISPLATIN	0	5 (13.5%)	5 (9.4%)
NIVOLUMAB	0	3 (8.1%)	3 (5.7%)
CRIZOTINIB	0	2 (5.4%)	2 (3.8%)
DOCETAXEL	0	2 (5.4%)	2 (3.8%)
GEMCITABINE	0	2 (5.4%)	2 (3.8%)
PACLITAXEL	0	2 (5.4%)	2 (3.8%)
PEMETREXED DISODIUM	0	2 (5.4%)	2 (3.8%)
BEVACIZUMAB	0	1 (2.7%)	1 (1.9%)
ERLOTINIB	0	1 (2.7%)	1 (1.9%)
DRUGS FOR TREATMENT OF BONE DISEASES			
Patients with Anti-Cancer Treatment Administered After Progression by BICR RECIST Assessment	0	1 (2.7%)	1 (1.9%)
DENOSUMAB	0	1 (2.7%)	1 (1.9%)
No Coding available			
Patients with Anti-Cancer Treatment Administered After Progression by BICR RECIST Assessment	2 (28.6%)	0	2 (3.8%)
No Coding available	2 (28.6%)	0	2 (3.8%)

Multiple uses of a specific treatment for a patient were counted once in the frequency for the treatment. Likewise, multiple uses within a specific treatment class for a patient were counted once in the frequency for the treatment class.

B12. Priority: Please provide the same details requested in B11 for patients in the ERG's preferred efficacy set (defined in A3).

Please see Table 29 for a breakdown of the subsequent therapies received by patients in the ERG's preferred efficacy set. Please note the data in Table 29 does not exactly match the data in Figure 9 due to the data being more recent and the cleaning of the data.

Table 29: Summary of subsequent anti-cancer systemic therapies, ERG preferred efficacy set (N=78)

WHO ATC Level 2 (Therapeutic Class)	Coded name	n patients	% patients
Antineoplastic Agents	Any	[redacted]	[redacted]

WHO ATC Level 2 (Therapeutic Class)	Coded name	n patients	% patients
Antineoplastic Agents	Crizotinib	[redacted]	[redacted]
Antineoplastic Agents	Carboplatin	[redacted]	[redacted]
Antineoplastic Agents	Pemetrexed	[redacted]	[redacted]
Antineoplastic Agents	Lambrolizumab	[redacted]	[redacted]
Antineoplastic Agents	Protein kinase inhibitors	[redacted]	[redacted]
Antineoplastic Agents	Bevacizumab	[redacted]	[redacted]
Antineoplastic Agents	Cabozantinib	[redacted]	[redacted]
Antineoplastic Agents	Cisplatin	[redacted]	[redacted]
Antineoplastic Agents	Gemcitabine	[redacted]	[redacted]
Antineoplastic Agents	Paclitaxel	[redacted]	[redacted]
Antineoplastic Agents	Pemetrexed Disodium	[redacted]	[redacted]

B13. Priority: Please clarify if ALKA or STARTRK-1 collected data on subsequent treatments and if so, please provide the same details requested in B11 and B12, separately.

Please see Figure 9 for the subsequent therapy data reported in STARTRK-1.

As far as we are aware, no subsequent therapy data was collected in ALKA, as there is no post-treatment systemic cancer data for this study. Table 14.1.13.2, page 206 of the ALKA CSR reports the concomitant medications, however the table is not split by cancer therapies. For further details on why there is no data on anti-cancer therapy for patients in the ALKA study, please refer to the ALKA CSR, page 6180 and page 6171 for further details (reference 40).

Page 6171: **Concomitant Medication**: “All concomitant medications should be reported in the relevant eCRF, including supportive care drugs, and drugs used for treating adverse events or chronic diseases. In the follow-up, if an alternative anticancer therapy is initiated, the reporting of the concomitant medication is no further requested”.

Page 6180 Section 9.2.7.6. **Other anticancer or experimental therapy:** “No other approved or investigational anticancer treatment will be permitted during the study

period, including chemotherapy, immunotherapy, biological response modifiers, hormones".

B14. The CS reports (page 149) that data on subsequent treatments were collected from entrectinib trials and adjusted to reflect clinical experts' opinion. Please quantify the changes made to the data based on clinical experts' opinion. Please explain why only approximately 64% of patients received subsequent treatment in the model.

Table 30 reports the subsequent therapies received as reported in the clinical trials versus the proportions assumed for each subsequent therapy in the model, for each treatment arm. The adjustments made based on clinical opinion were:

- Clinical opinion stated that patients receiving pemetrexed plus platinum would not receive further pemetrexed plus platinum, so the proportion receiving pemetrexed, cisplatin and carboplatin was assumed to be 0%.
- Clinical opinion stated that patients receiving crizotinib would not receive further crizotinib after progression, so the proportion receiving crizotinib as a subsequent therapy was assumed to be 0%.
- In line with the NICE position on therapies in the CDF, crizotinib is not included as a subsequent therapy following entrectinib in the base case comparison to pemetrexed plus platinum (assumed 0% would receive crizotinib)

Table 30 reports the proportion of patient receiving each subsequent therapy, as reported in the entrectinib clinical trials. The proportion of patients receiving each type of subsequent therapy was used to estimate the weighted cost. Not all patient's subsequent therapy after progression was reported in the entrectinib clinical trials (and some patients received more than one type of therapy).

Table 30: Subsequent therapies used in the model

	Clinical trials n=[redacted] n (%)	% entrectinib arm vs. pemetrexed	% Pemetrexed plus platinum therapy arm	% entrectinib arm vs. crizotinib	% crizotinib arm (adjusted based on

		(adjusted based on clinical opinion)	(adjusted based on clinical opinion)	(adjusted based on clinical opinion)	clinical opinion)
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B15. Given the company's use of pemetrexed + platinum therapy outcomes in ALK+ patients as a proxy for ROS1+ patients, can the company please provide the ALK+ outcomes (particularly OS and PFS data) from STARTRK-2 for entrectinib for comparison with ROS1+ outcomes.

The comparison of ALK+ outcomes with ROS1+ outcomes from STARTRK-2 specifically, is an uninformative analysis due to the difference in patient populations. Only 7 ALK+ patients in the STARTRK-2 efficacy set had NSCLC, all of which had CNS progression while on crizotinib. Therefore, the populations aren't comparable. (Please refer to the STARTRK-2 CSR for further details, section 5.3.3, reference 42). Furthermore, a KM curve based on 7 patients is of limited use.

We recognise the limitations of using ALK+ data as a proxy for ROS1+ patients, hence our preference for the model base case for the comparison to pemetrexed + platinum was to use the PROFILE 1014 hazard ratio as opposed to the MAIC, which requires an assumption of comparable relative treatment effect rather than comparable absolute treatment effect across these patient groups.

Health-related quality of life

B16. Priority: Please complete (and expand) the following table to provide the total number of patients who completed the EQ-5D questionnaire at each follow-up time in the STARTRK-2 trial, along with the mean utility scores and standard deviations for those patients at each time. Please do this for each of the following:

a) **The primary efficacy set which forms the basis for the MAIC in the company's base case analysis;**

b) **All STARTRK-2 patients in the ERG's preferred efficacy set (defined in A3).**

Table 31: Patients who completed the EQ-5D questionnaire at each follow-up time in STARTRK-2

Population	Treatment cycle/follow-up	Number of patients completing EQ-5D	Mean EQ-5D score	Standard deviation
Original	Cycle 1 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 1 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 2 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 3 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 4 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 5 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 6 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 7 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 8 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 9 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 10 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 11 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 12 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 13 Day 1	[redacted]	[redacted]	[redacted]

Original	Cycle 14 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 15 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 16 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 17 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 18 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 19 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 20 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 21 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 22 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 23 Day 1	[redacted]	[redacted]	[redacted]
Original	Cycle 24 Day 1	[redacted]	[redacted]	[redacted]
Original	End Of Treatment	[redacted]	[redacted]	[redacted]
ERG	Cycle 1 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 2 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 3 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 4 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 5 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 6 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 7 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 8 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 9 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 10 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 11 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 12 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 13 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 14 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 15 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 16 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 17 Day 1	[redacted]	[redacted]	[redacted]

ERG	Cycle 18 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 19 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 20 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 21 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 22 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 23 Day 1	[redacted]	[redacted]	[redacted]
ERG	Cycle 24 Day 1	[redacted]	[redacted]	[redacted]
ERG	End Of Treatment	[redacted]	[redacted]	[redacted]

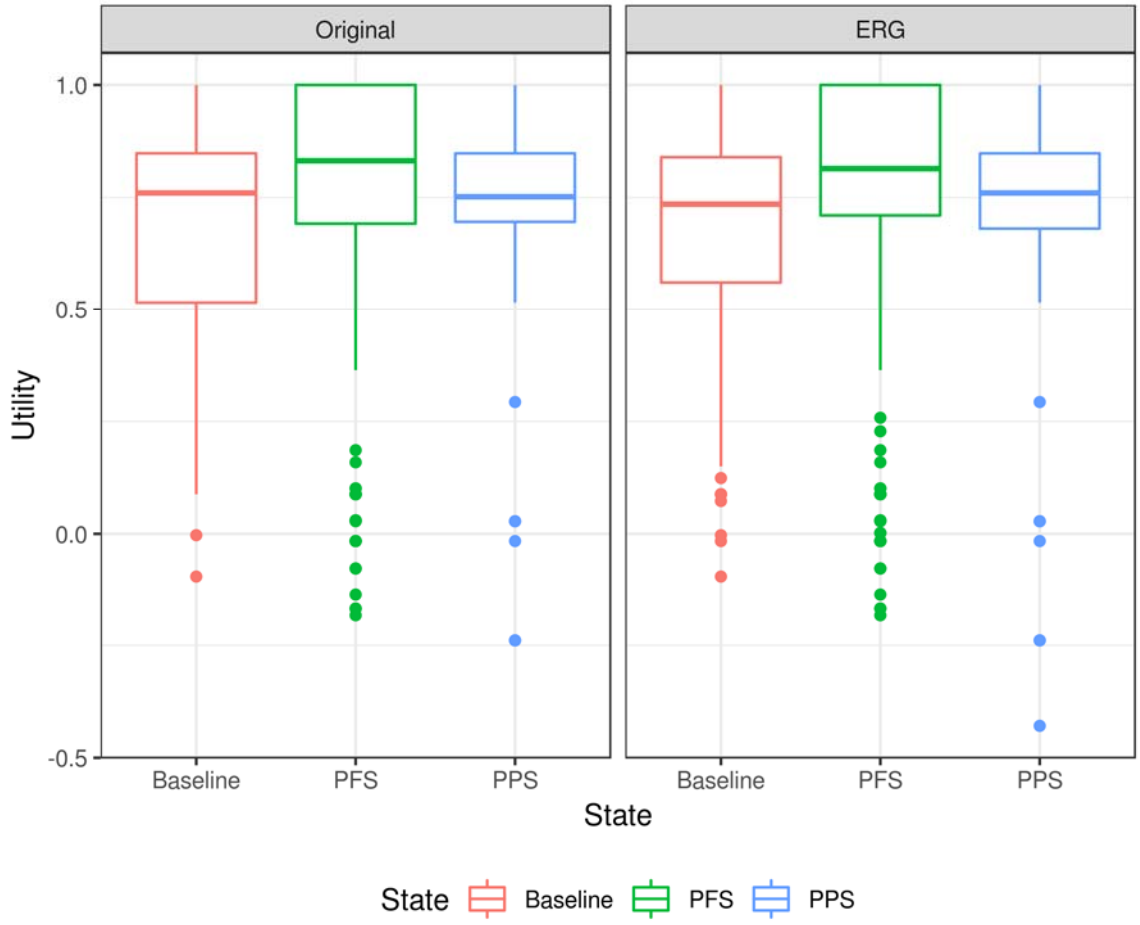
Table 31 provides the total number of patients who completed the EQ-5D questionnaire at each follow-up time in the STARTRK-2 trial, along with the mean utility scores and standard deviations for those patients at each time, in the primary efficacy set followed by the ERG's preferred efficacy set. Please note the primary efficacy data is from the latest day-75 FDA data cut (COOD 31 October 2018).

As EQ-5D in the submission was analysed by health state and not by visit, we have included the below box plot (Figure 10) and summary table (Table 32) which demonstrates there are no differences between the primary efficacy set and the ERG's preferred efficacy set.

Table 32: Summary of utility data

Population	State	n	mean_utility	sd
Original	Baseline	[redacted]	[redacted]	[redacted]
Original	PFS	[redacted]	[redacted]	[redacted]
Original	PPS	[redacted]	[redacted]	[redacted]
ERG	Baseline	[redacted]	[redacted]	[redacted]
ERG	PFS	[redacted]	[redacted]	[redacted]
ERG	PPS	[redacted]	[redacted]	[redacted]

Figure 10: Summary of utility data



B17: Priority. Please provide a breakdown of the linear regression results used in the company's base case analysis for the EQ-5D data from STARTRK-2 for each stage in the stepwise selection procedure.

a) **Please provide the coefficients and p-values for each variable included in the initial specified model;**

b) **Please provide the updated set of coefficients and p-values at each stage after removal of a variable;**

c) **Please specify the threshold for removing a variable from the model at each stage.**

Please see below a summary of the original regression stepwise selection in Figure 11, and a summary of the original regression coefficients in Table 33.

Figure 11: Summary of original regression stepwise selection

Output

```
Backward reduced random-effect table:

                              Eliminated npar logLik     AIC    LRT Df
Pr(>Chisq)
<none>                                     9 135.05 -252.09
QSYR in (1 + QSYR | USUBJID)          0    7 129.92 -245.84 10.253  2
0.005937 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Backward reduced fixed-effect table:
Degrees of freedom method: Satterthwaite

          Eliminated   Sum Sq  Mean Sq NumDF   DenDF F value Pr(>F)
I(SEX)             1 0.006370 0.006370     1 26.4999  0.3547 0.5565
I(EXTENT)          2 0.012750 0.012750     1 24.3024  0.7096 0.4078
AGE                3 0.020586 0.020586     1 29.3382  1.1448 0.2934
QSYR               4 0.059649 0.059649     1  9.1808  3.3178 0.1012

Model found:
AVAL_GBR ~ (1 + QSYR | USUBJID)
```

Table 33: Summary of original regression coefficients by step

Variable	Step_0	Step_1	Step_2	Step_3	Step_4
(Intercept)	0.668	0.743	0.484	[redacted]	[redacted]
AGE	0.006	0.005	0.005		
I(EXTENT)METASTATIC DISEASE	-0.218	-0.257			
I(SEX)M	-0.068				
QSYR	-0.092	-0.085	-0.089	-0.080	

B18. Priority: Please provide further explanation as to how the correlation between repeated measures of EQ-5D scores has been accounted for in the linear model. With the limited detail provided in the CS regarding the

regression analysis, the ERG is unsure whether this issue has been appropriately addressed.

A linear mixed model was fit using the package lme4 in R. Only data for patients in the progression free health state were included in the analysis (excluding baseline and measurements post progression). To account for correlation between measurements, the final model included random effects for patients both on the intercept and slope (with slope defined considering time in years). For selection thresholds the lmertest default thresholds were used (0.1 for random effects and 0.05 for fixed effects). For the specific code used and further details please see below the answer to B19.

B19. Priority: Please provide the code used to run the linear model for EQ-5D data.

```
library(lme4)

library(lmertest)



# AVAL = utility using uk value set

# QSYR = date of measurement in years from baseline (scaled for better convergence)

# SEX = M vs F

# AGE = age at baseline in years

# EXTENT = locally advanced vs Metastatic

# State = PFS, PPS, Baseline (defined by comparng measurement time to PFS duration)



ros1lung.full <- lmer(AVAL ~ 1 + (1+QSYR|USUBJID) + QSYR + I(SEX) + AGE + I(EXTENT),
```

REML = TRUE, data = ros1.df, subset = State == "PFS")

ros1lung.step = step(ros1lung.full)

ros1lung.final <- lmer(AVAL ~ 1 + (1+QSYR|USUBJID) ,

REML = TRUE, data = ros1.df, subset = State == "PFS")

B20. Priority: Please perform an additional EQ-5D regression analysis, with the same stepwise selection procedure applied, to include patients in the ERG's preferred efficacy set (defined in A3).

a) **Please provide the coefficients and p-values for each variable included in the initial specified model;**

b) **Please provide the updated set of coefficients and p-values at each stage after removal of a variable;**

c) **Please specify the threshold for removing a variable from the model at each stage.**

The EQ-5D regression analysis with the ERG's preferred efficacy did change the results. While the stepwise selection changed, the final model and coefficients were the same, with a PFS utility of [redacted] See Figure 12 and Table 34.

Figure 12: Summary of ERG regression stepwise selection

Output

```
Backward reduced random-effect table:

                            Eliminated npar logLik     AIC    LRT Df
Pr(>Chisq)
<none>                                   9 292.84 -567.69
QSYR in (1 + QSYR | USUBJID)          0    7 283.36 -552.73 18.962  2
7.631e-05 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Backward reduced fixed-effect table:
Degrees of freedom method: Satterthwaite

          Eliminated    Sum Sq   Mean Sq NumDF  DenDF F value Pr(>F)
I(SEX)             1 0.0000007 0.0000007     1 49.393  0.0000 0.9947
QSYR               2 0.0003341 0.0003341     1 25.410  0.0218 0.8839
AGE                3 0.0030195 0.0030195     1 53.191  0.1964 0.6594
I(EXTENT)          4 0.0169254 0.0169254     1 44.823  1.1004 0.2998

Model found:
AVAL_GBR ~ (1 + QSYR | USUBJID)
```

Table 34: Summary of ERG regression coefficients by step

Variable	Step_0	Step_1	Step_2	Step_3	Step_4
(Intercept)	0.668	0.743	0.795	[redacted]	[redacted]
AGE	0.006	0.005	0.004		
I(EXTENT)METASTATIC DISEASE	-0.218	-0.257	-0.267	-0.267	
I(SEX)M	-0.068				
QSYR	-0.092	-0.085			

B21. Please provide three scenario analyses using each of the following data sources to simultaneously inform both PFS and PPS health state utilities for consistency in the model:

a) **PROFILE 1007**

b) **PROFILE 1014**

c) ALEX

These scenarios have been implemented in the cost-effectiveness model (19.07.17_ Entrectinib_ROS1NSCLC_ERG preferred efficacy set_CEM) and can be selected using the dropdown menu in cells F47:F49 in the “Model Inputs” sheet.

The results of the requested scenarios are presented in Table 35. All scenarios have been run using the ERG’s preferred efficacy set and include the amendments requested in B26 and B27. For all scenarios, in line with the assumption made in the submission, it is conservatively assumed that all treatment arms will have the same utility value.

For PROFILE 1007, the pre-progression utility was sourced from Blackhall et al 2014.[2] The post-progression utility from PROFILE 1007 is not clear from the available papers for TA422 or the literature. Page 16 of the TA296 reappraisal states “This post progression utility value is 0.61 for both, unchanged from the value in the original model.” Therefore, a scenario has been included which assumes a post-progression utility of 0.61. Given the uncertainty, a scenario has also been presented where a post-progression utility of 0.47 is assumed; this aligns with the assumptions made in TA529 for the subsequent treatment line.

Pre-progression utilities for PROFILE1014 were sourced from TA406 (Final appraisal determination). Post-progression utilities from PROFILE1014 are not reported in TA406 or in the literature. Therefore, in line with TA406, post-progression utility is sourced from PROFILE1007.

The pre-progression and post-progression utilities from the ALEX clinical trial were sourced from TA536 (ERG report, Table 21). In TA536, the committee preferred sourcing post-progression utilities from Roughley et al. 2014[3] – a further scenario is presented using this value.

As illustrated in Table 35, using alternative utility sources did not have a significant impact on model outcomes, resulting in an ICER that continually fell well below the £50,000 willingness to pay threshold for end-of-life treatments. When sourcing PFS utility values from PROFILE 1007 and using a PPS utility of 0.47 from Nafees et al.

2008[4], the biggest increase in the ICER was observed (£26,359/QALY) as a result of the low utility value compared with the model base case (0.47 vs. 0.66).

Table 35: Alternative health state utility values scenario analyses for entrectinib (with PAS) versus pemetrexed plus platinum (list price) and crizotinib (list price)

	Utility values used	Source	ICER (£/QALY): entrectinib versus crizotinib	ICER (£/QALY): entrectinib versus pemetrexed plus platinum therapy
Base case	PFS: 0.73 PPS: 0.66	STARTRK PROFILE1007 (reported PFS utility for patients on chemotherapy)	Entrectinib is dominant	21,628
a)	PFS: 0.82 PPS: 0.61	PROFILE1007 (Blackhall et al, 2014) PROFILE1007 (TA296 reappraisal committee papers, page 16)	Entrectinib is dominant	22,144
	PFS: 0.82 PPS: 0.47	PROFILE1007 Nafees et al.	Entrectinib is dominant	26,359
b)	PFS: 0.81 PPS: 0.66	PROFILE1014 (TA406 FAD) TA406	Entrectinib is dominant	21,021
c)	PFS: 0.81 PPS: 0.73	ALEX (TA536, ERG report, Table 21)	Entrectinib is dominant	19,612
	PFS: 0.81 PPS: 0.65	ALEX Roughley et al. (preferred PPS utility by committee in TA536)	Entrectinib is dominant	21,222

Key: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal; FAD, final appraisal determination.

B22. The ERG considers the use of standard gamble-derived disutilities for adverse events combined with EQ-5D based health state utilities to be inconsistent. Please consider using alternative sources of adverse event data in an alternative but similar population e.g. ALK-positive patients.

All previous ALK-positive NSCLC technology appraisals (TA406, TA536 and TA571) sourced adverse event disutilities from Nafees et al, 2008[4], which uses standard gamble techniques, when including adverse event disutilities in their analysis. No relevant alternative utility decrements have been identified for ALK-positive or ROS1-

positive NSCLC patients. Therefore, the disutilities from Nafees et al, 2008 are considered the most appropriate values, based on the data available.

In the previous technology appraisals in ALK-positive and ROS1-positive NSCLC, it was assumed in the base case that the health state utility values already reflect any negative changes in utility incurred through the adverse event profiles of the treatments. Therefore, a scenario has been included where adverse event disutilities and costs have been excluded further investigating the impact of the exclusion of adverse events on model results.

The scenario has been run using the ERG's preferred efficacy set and includes the amendments requested in B26 and B27. The results are reported in Table 36 and Table 37. This scenario results in minimal impact on the ICERs (21,914 vs. 21,628 base case ICER [£/QALY]).

Table 36: Base case results: entrectinib (with PAS) versus pemetrexed plus platinum (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base case ICER (£/QALY)
Pemetrexed plus platinum	20,327	1.23	0.88					
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,914	21,628

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 37: Key scenario results: entrectinib (with PAS) versus crizotinib (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]				
Crizotinib	128,911	3.17	2.22	[redacted]	[redacted]	[redacted]	Entrectinib is dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

B23. The CS refers to scenario analyses conducted using alternative utility values (for example, page 136 of the CS). However, the ERG could not find the results of such analyses either in the CS or in the economic model. Please update the economic model to include these scenario analyses and report the results of each scenario.

The results of the scenarios where alternative utility assumptions are tested are provided as part of the response to Question B21 and Question B22.

Costs

B24. Priority: Please include an option in the economic model to apply pemetrexed maintenance therapy costs after treatment with both carboplatin and cisplatin, given that maintenance with pemetrexed after treatment with carboplatin is now part of current clinical practice. Please provide this analysis for all the following scenarios:

a) **Company's base case effectiveness assumptions for pemetrexed + platinum therapy (HR from PROFILE 1014):**
    i. **Assuming 4 cycles of maintenance therapy;**
    ii. **Assuming maintenance therapy with pemetrexed is given until progression;**
b) **Company's scenario analysis using the ASCEND-4 MAIC results to estimate effectiveness for pemetrexed + platinum therapy:**
    i. **Assuming 4 cycles of maintenance therapy;**
    ii. **Assuming maintenance therapy with pemetrexed is given until progression;**
    iii. **No pemetrexed maintenance therapy costs.**

The requested scenarios have been implemented in the model (19.07.17_ Entrectinib_ROS1NSCLC_ERG preferred efficacy set_CEM) in cells D85-89 in the "Cost Inputs" sheet. If the option of applying maintenance therapy is selected (cell D85 in the "Cost Inputs" sheet), three additional options will appear in cells D86-D89.

In cell D86, the user has the choice to apply maintenance therapy after both carboplatin and cisplatin or use the model base case where pemetrexed maintenance therapy is only applied to patients who have received pemetrexed in combination with cisplatin. In addition, the model has the functionality of applying maintenance therapy for a limited number of cycles, where the number of cycles can be specified in cell D88. Otherwise, pemetrexed maintenance therapy is applied until progression.

The results of the scenario analyses are presented in Table 38. All scenarios have been run on the ERG's preferred efficacy set, assuming treatment after both carboplatin and cisplatin along with the requested amendments in B26 and B27.

Using the model base case, where the HR from PROFILE 1014 is used to estimate the pemetrexed plus platinum arm, applying pemetrexed maintenance therapy for a maximum of 4 cycles or until progression results in a decrease in the ICER compared with the base case (£19,422/QALY vs. £21,628/QALY) and (£12,347/QALY vs. £21,628/QALY), respectively.

When using the alternative scenario, where the HRs from the updated ASCEND-4 MAIC versus entrectinib is used, applying pemetrexed maintenance therapy for a maximum of 4 cycles or until progression results in a decrease in the ICER compared with the alternative scenario base case (£44,004/QALY vs. £47,634/QALY and £24,992/QALY vs. £47,634/QALY, respectively). However, when no pemetrexed maintenance therapy is applied, this results in an increase in the ICER above the WTP of £50,000 compared with the alternative base case scenario (£51,896/QALY vs. £47,634/QALY).

Table 38:Results of scenario analysis: entrectinib (with PAS) versus pemetrexed plus platinum (list price)

Effectiveness Data used	Scenario	ICER (£/QALY): entrectinib versus pemetrexed plus platinum therapy
Base case effectiveness assumptions for pemetrexed + platinum therapy (HR from PROFILE 1014)	Base case: No pemetrexed maintenance therapy costs.	21,628
	Assuming 4 cycles of maintenance therapy	19,422

Effectiveness Data used	Scenario	ICER (£/QALY): entrectinib versus pemetrexed plus platinum therapy
	Assuming maintenance therapy with pemetrexed is given until progression	12,347
Scenario analysis using the ASCEND-4 MAIC results to estimate effectiveness for pemetrexed + platinum therapy	Alternative scenario base case: Assuming 4 cycles of pemetrexed maintenance therapy post pemetrexed in combination with cisplatin	47,634
	Assuming 4 cycles of maintenance therapy	44,004
	Assuming maintenance therapy with pemetrexed is given until progression;	24,992
	No pemetrexed maintenance therapy costs.	51,896
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison.		

B25. Priority: Please provide scenario analyses in which pemetrexed plus platinum-based chemotherapy is given to all patients as a subsequent treatment after 1st line crizotinib or entrectinib.

The scenario can be selected in the model using the dropdown menu in cell D196 in the "Cost Inputs" sheet of the cost-effectiveness model (19.07.17_Entrectinib_ROS1NSCLC_ERG preferred efficacy set_CEM).

The results when assuming platinum-based chemotherapy is given to all patients as a subsequent treatment, following entrectinib or crizotinib are presented in Table 39 and Table 40 for the comparison to pemetrexed plus platinum and crizotinib, respectively. All results have been run using the ERG's preferred efficacy set, with the amendments requested in B26 and B27 included. The subsequent therapies for the pemetrexed plus platinum arm are assumed to be the same as those in the original submitted model (clinical trial, adjusted for clinical opinion). This amendment results in a slight increase in the ICER versus pemetrexed plus platinum therapy (~£674/QALY).

Table 39: Base case results: entrectinib (with PAS) versus pemetrexed plus platinum (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Base case ICER (£/QALY)
Pemetrexed plus platinum	20,867	1.23	0.87					
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,302	21,628

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 40: Key scenario results: entrectinib (with PAS) versus crizotinib (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]				
Crizotinib	129,696	3.17	2.22	[redacted]	[redacted]	[redacted]	Entrectinib is dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

B26. Priority: Subsequent treatment costs are applied as a one-off cost for all newly progressed patients but discounting is only applied based on the time patients progress. Consider applying discount factors that account for the greater discount factors that should apply to the later doses of subsequent treatments received.

In order to account for the greater discount factor applied to the later does of subsequent therapies, a different discounting rate has been applied to the subsequent therapy costs in (Sheets “Entrectinib ROS1”, “Crizotinib_ROS1” and “Chemotherapy_ROS1” in the cost-effectiveness model (19.07.17_ Entrectinib_ROS1NSCLC_ERG preferred efficacy set_CEM)) as a scenario. The switch for this scenario has been added to cell D204 of the “Costs Inputs” tab.

The discount rate is estimated using the following formula:

$$1/(1 + discount\ rate)\text{^}(t_0 + Max\ ToT/12)$$

Where t_0 is the start time (time of progression) and $\mathrm{Max\ ToT}$ is the end time (maximum duration of subsequent therapy).

The maximum duration of subsequent therapy for each arm is:

- 19.22 months for the entrectinib arm (when comparing to crizotinib)
- 11 months for the entrectinib arm (when comparing to pemetrexed plus platinum)
- 11 months for the pemetrexed plus platinum arm
- 11 months for the crizotinib arm

However, given that the maximum ToT duration from the basket of subsequent therapy for the majority of the treatment arms was less than a year, it was expected that this amendment would result in minimal impact on the ICERs:

- £21,628/QALY (ERG suggested discounting) vs. £21,650/QALY (company's original approach)

Other issues

B27. Please amend the half-cycle correction so that the first cycle begins with 100% of patients receiving the initial therapy dose. The second half-cycle should then be the midpoint of the first and second cycles and so on.

This amendment has been made in sheets "Entrectinib ROS1", "Crizotinib_ROS1" and "Chemotherapy_ROS1" in the cost-effectiveness model (19.07.17_ Entrectinib_ROS1NSCLC_ERG preferred efficacy set_CEM). The switch for this scenario has been added to cell F17 of the "Model Inputs" tab.

This amendment results in a slight increase in the ICERs:

- £21,628/QALY (ERG suggested half cycle correction) vs. £21,035/QALY (company's original approach)

References

1. Solomon BJ, Kim DW, Wu YL, et al. Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2018; 36(22):2251-8.

2. Blackhall F, Kim D-W, Besse B, et al. Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with ALK-Positive Advanced Non–Small-Cell Lung Cancer. *Journal of Thoracic Oncology*. 2014; 9(11):1625-33.

3. Roughley A, Damonte E, Taylor-Stokes G, et al. Impact of Brain Metastases on Quality of Life and Estimated Life Expectancy in Patients with Advanced Non-Small Cell Lung Cancer. *Value Health*. 2014; 17(7):A650.

4. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008; 6:84.

Appendix A

Figure 13: Overall survival KM curves - selected cohorts with different follow-up times

Figure 14: Progression-free survival KM curves - selected cohorts with different follow-up times

Appendix B

Table 41: OS KM: ERG Preferred Efficacy Set, clinical data cut: 31 October 2018

time	surv	lower	upper	nleft	nfailed	strata
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]			[redacted]	[redacted]	all=all

Table 42: PFS KM: ERG Preferred Efficacy Set, clinical data cut: 31 October 2018

time	surv	lower	upper	nleft	nfailed	strata
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]			[redacted]	[redacted]	all=all

Table 43: CNS PFS KM: ERG Preferred Efficacy Set, clinical data cut: 31 October 2018

time	surv	lower	upper	nleft	nfailed	strata
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
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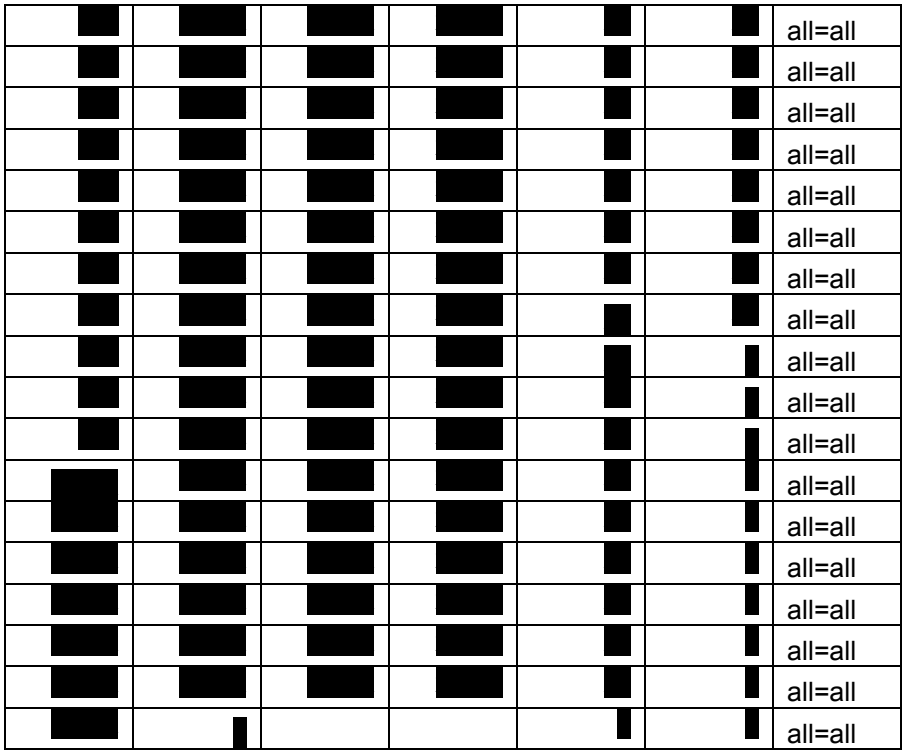
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	all=all



Appendix C

Table 44: OS KM data - Crizotinib - PROFILE 1001

Time_to_Event	nRisk	nEvents	Censoring	Survival
0	53	0	0	1
1.1196	53	1	0	0.986689
1.480505	52	0	0	0.974862
1.977231	52	1	1	0.965917
2.835671	50	0	0	0.95742
3.694112	50	1	0	0.948922
3.813539	49	0	0	0.938107
4.510573	49	1	0	0.920452
5.088553	48	1	0	0.909267
5.904381	47	0	0	0.898723
6.5646	47	1	0	0.890383
6.762151	46	0	0	0.880056
7.423524	46	1	1	0.859725
8.590499	44	1	0	0.849972
9.699438	43	1	0	0.832474
10.59072	42	0	0	0.820955
11.48074	42	2	0	0.7903
11.97575	40	0	0	0.781803
12.47077	40	1	0	0.773305
13.03148	39	0	0	0.759001
13.59258	39	1	0	0.750645
13.92234	38	0	0	0.741046

14.35135	38	1	0	0.73365
14.88545	37	0	0	0.724068
15.63873	37	1	0	0.716654
17.22224	36	1	0	0.681183
18.87339	35	1	1	0.669445
23.46524	33	0	2	0.661892
25.06707	31	1	0	0.653867
25.91981	30	0	2	0.642327
28.61038	28	0	0	0.640694
29.87184	28	1	0	0.61846
30.36692	27	1	0	0.610906
30.56241	26	1	0	0.569363
32.05886	25	1	1	0.549745
34.22836	23	0	0	0.549299
35.18528	23	1	1	0.531218
38.52174	21	0	0	0.524815
39.11589	21	1	0	0.516489
40.55453	20	0	0	0.497742
44.03737	20	0	0	0.497605
51.50357	20	1	0	0.490052
53.00013	19	0	1	0.472165
56.45816	18	0	1	0.472112
65.64284	17	0	0	0.471989
66.30306	17	1	0	0.463615
67.11552	16	1	0	0.425847
71.1897	13	0	0	0.41735

Table 45: PFS KM data - Crizotinib - PROFILE 1001

Time_to_Event	nRisk	nEvents	Censoring	Survival
0	53	0	0	1
0.049881	53	1	0	0.989178
1.048878	52	0	0	0.976982
1.50453	52	1	0	0.965497
1.680565	51	1	1	0.951787
1.760552	49	0	0	0.939947
1.944534	49	1	0	0.931846
2.076518	48	0	0	0.921875
2.376453	48	1	0	0.911904
2.688829	47	0	0	0.901933
3.16975	47	1	0	0.8876
3.175482	46	0	1	0.881022
3.939205	45	1	0	0.864792
4.248298	44	1	0	0.854572
4.568968	43	0	0	0.844601
4.570323	43	1	0	0.83463
4.571679	42	0	0	0.82466
4.573034	42	1	0	0.814689
4.87919	41	0	0	0.804718
5.141803	41	1	0	0.794747
5.288583	40	0	0	0.782699

6.495165	40	1	0	0.768765
6.496207	39	0	1	0.761096
7.895447	38	1	0	0.744633
8.633368	37	1	1	0.734922
8.780148	35	0	0	0.722874
10.41991	35	1	0	0.7023
12.32147	34	1	1	0.689954
13.47373	32	0	0	0.682717
14.65173	32	1	0	0.665483
14.65304	31	0	0	0.655868
14.94283	31	1	0	0.643076
15.26578	30	0	0	0.632721
15.26714	30	1	0	0.62275
15.26849	29	0	0	0.61278
15.45003	29	1	0	0.598602
15.83794	28	1	0	0.587853
16.05701	27	0	0	0.577882
16.23254	27	0	0	0.567911
16.37943	27	1	0	0.555032
16.88907	26	1	0	0.542984
16.89029	25	0	0	0.53401
18.11064	25	1	0	0.515866
19.28901	24	0	0	0.505593
19.32926	24	1	0	0.494238
19.46589	23	0	0	0.485652
19.72851	23	1	0	0.475681
20.90083	22	0	0	0.464602
21.60308	22	1	0	0.453002
21.99675	21	0	1	0.446194
24.83623	20	1	0	0.430667
26.44157	19	0	0	0.420841
27.58656	19	1	0	0.406197
29.05753	18	0	0	0.395914
29.909	18	1	0	0.383262
31.1071	17	0	0	0.37348
33.15497	17	1	0	0.363509
39.16779	16	1	1	0.334843
40.37402	14	1	0	0.313768
40.54985	13	1	1	0.286383
48.75773	11	1	0	0.257569
50.72089	10	1	0	0.23015

NICE National Institute for Health and Care Excellence

Professional organisation submission

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

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-NCRI-ACP-RCP-RCR

3. Job title or position	
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).	BTOG-NCRI-ACP-RCP-RCR
5b. 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,	The main aims of the treatment are to control disease through tumour response/ delaying time to tumour progression and to prolong survival. The aim also is to achieve control of brain metastases.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Our experts would consider a reduction in tumour size by more than 30% as being clinically significant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Current treatment for ROS1 positive lung cancer is with crizotinib, a multi-targeted kinase inhibitor directed against ROS1/ALK and cMET. Crizotinib has limited activity in the brain yet brain metastases are a significant problem in this patient population. According to a single site experience of ROS1 non-small cell lung cancer patients being treated with crizotinib, approximately one third of patients had brain metastases at presentation and 47% patients developed brain metastases as their first and only site of metastasis during treatment (Patil *et al.* J Thorac Oncol 13:1717-26, 2018). Entrectinib has 40x more potency against ROS1 *in vitro* and was designed with the ability to cross the blood-brain barrier (Ardini *et al.* Mol Cancer Ther 15:628-39, 2016)
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Since NICE Technology appraisal guidance [TA529] in July 2018, the standard of care treatment for ROS1 fusion positive NSCLC has become crizotinib. Prior to that ROS1 NSCLC patients were treated with standard chemotherapy (typically platinum-pemetrexed in the first-line setting and docetaxel +/- nintedanib in the second line setting and/or immunotherapy, as per guidance in unselected non-squamous NSCLC populations)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	As above.
• 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.)	Clinicians are in agreement that treatment with a ROS1 inhibitor is appropriate for patients with ROS1 fusion positive disease, akin to the management of patients with EGFR or ALK alterations with respective inhibitors. The pathway of care, however, depends on routine screening for the ROS1 alteration. Prior to the introduction of the NICE Technology appraisal guidance [TA529], screening for ROS1 alteration was highly variable between centres, predominantly being performed in research active centres with available clinical trials. Without testing, patients would have received standard chemotherapy. Since the introduction of NICE guidance for use of crizotinib, screening for ROS1 has now become more routine.The usual approach is for IHC testing in the first instance followed by confirmatory FISH on positive cases. In time this may change to next generation nucleic acid-based sequencing as genomics become more established in routine care

• What impact would the technology have on the current pathway of care?	There should be no significant impact on the current pathway of care as ROS1 screening has become more routine.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• 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 clinics.)	Entrectinib should only be prescribed by oncologists in the secondary/tertiary care setting.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It may be useful to ensure ROS1 testing is performed to quality controlled standards and equitably across the NHS - this may be addressed by the introduction of the Genomics Test Directory and re-designation of the Genomic Laboratory Hubs. Given the absence of randomised controlled clinical trial data it would also be important to set-up a database to ensure outcome data are collected across the NHS for all patients treated with entrectinib for real-world data collection.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, please see detail below.
• Do you expect the technology to increase length of life more than current care?	Yes. The reported data for crizotinib (current standard-of-care) show a median PFS of 19 months in PROFILE 1001 and 15.9 months in OxOnc (East Asian population). Median overall survival was 51.4 months and 32.5 months, respectively. It is important to note that the PROFILE1001 trial did not report whether patients had brain metastases. In the OxOnc study, 18% patients had brain metastases at baseline. For OxOnc the median PFS was 10.2 months for patients with brain metastases and 18.8 months for patients without. Interestingly, the median PFS of patients treated with crizotinib in the real-world setting

	is only 9-12 months (Mazieres *et al.,* J Clin Oncol 33; 992-9, 2015; Patil *et al.* J Thorac Oncol 13:1717-26, 2018) In the entrectinib trials, 40% patients had brain metastases at study entry, implying a poorer prognostic group. Despite this, median PFS was 19 months (13.6 months in patients with brain metastases and 26.3 months in patients without). Median OS has not been reached in the entrectinib trials.
• Do you expect the technology to increase health-related quality of life more than current care?	The time to treatment response is reportedly quicker with entrectinib (compared with crizotinib) although this may be a result of timings of CT scans performed on the respective clinical trials. From first-hand experience in using entrectinib there has been very rapid improvement in disease related symptoms and overall the drug is well-tolerated. The impact of reducing brain metastases has also been very apparent with improvement in neurological symptoms. In addition, to delay the onset of brain metastases is very important in the context of health-related quality of life both physically and emotionally. There is also impact on driving and independence which are important factors in a patient's QoL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Entrectinib would only be effective in patients with an activating ROS1 fusion (or ALK/NTRK fusion which is outside the scope of this appraisal). The data support that entrectinib is also beneficial in patients with brain metastases (in ROS1 positive NSCLC). Using crizotinib, approximately half of treated patients develop brain metastases, usually within 12 months of treatment. In the entrectinib studies, for those patients with brain metastases at baseline (40% of the population) intracranial response rate was 55% demonstrating clear CNS activity. The median time to CNS progression in those without baseline brain mets has not yet

	been reached implying the time to brain metastases may be delayed. This could have significant QoL impact as detailed above.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The treatment is similar to other small molecule targeted therapies so should not be challenging in terms of treatment administration. It is an oral therapy administered once daily. There are no unusual additional clinical requirements outside of the genomic pre-screening required. The side-effect profile is easily manageable. It may be worth considering baseline brain imaging for all patients with ROS1 positive disease for the purpose of disease monitoring that is currently outside standard practice for asymptomatic patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Pre-screening of NSCLC patients (likely just non-squamous) for ROS1 fusion is required for treatment selection.

Do these include any additional testing?	Stopping rules would be according to standard practice in terms of radiological or clinical progression or unacceptable toxicity. There is scope to continue dosing beyond progression if there is slow progression or single sites of progression amenable to localised therapy.
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?	The QALY calculation should cover the potential benefits
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?	Lung cancer has become a disease of multiple molecular sub-types and there has been very clear and tangible benefits in using molecularly targeted therapies. ROS1 fusion represents 1-2% of the NSCLC (non-squamous) population and there is no doubt that targeting this molecular driver results in clear patient benefit. To date, crizotinib is the only agent available for targeting this pathway but was not designed initially as a specific ROS1 inhibitor, therefore, has less specificity for the target. Entrectinib is a multikinase inhibitor but selectively inhibits ROS/ALK/TRK and has 40x greater affinitiy for the ROS1 target than crizotinib. The data to date support the superior efficacy of entrectinib although it is extremely challenging to undertake a randomised controlled trial to compare the agents due to the low prevalence of the alteration

	and time that would be required to undertake such a study. Nonetheless, there is clear evidence for the CNS activity which could provide a step-change in the management of this condition and reduce morbidity.
• Is the technology a 'step-change' in the management of the condition?	See above.
• Does the use of the technology address any particular unmet need of the patient population?	The CNS penetration of the drug is particularly relevant. The management of patients with brain metastases in lung cancer remains a significant problem and this drug has demonstrable activity in controlling existing brain mets and delaying onset of CNS metastases. This is in addition to longer extracranial PFS than reported with crizotinib. .
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is tolerable. Some patients require a dose reduction or interruption but rarely need to discontinue due to toxicity (5% in clinical trials). Main toxicities from first-hand experience include altered taste, weight gain, transient mild neurological side effects (such as dizziness, paraesthesia). The impact of improvement in disease related symptoms has outweighed the mild toxicities.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Three clinical trials have evaluated entrectinib in patients with ROS1 (and ALK/NTRK) fusion positive disease: ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267). These studies have enrolled patients across 150 sites in 15 countries including the UK. All were single arm studies. There are no control arms to compare with UK practice. However, patients were treated either in the first, second or third or more line setting reflecting the spectrum of patients who may be treated in the UK. Demographics were representative of the UK population.
• If not, how could the results be extrapolated to the UK setting?	The endpoints used in the single arm studies would need to be compared with historical data of comparators in the UK (crizotinib/chemotherapy/immunotherapy) although it is unlikely the prevalence of ROS1 fusion is detailed in chemotherapy and immunotherapy studies as this was not standard of care testing at the time.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate, progression free survival, intracranial activity (including RR and time to intracranial progression) and overall survival. All these parameters were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS is likely to reflect long-term clinical outcomes given the degree of response and PFS seen and extrapolating from management of other genomically driven cancers such as EGFR and ALK positive

	disease. Overall survival is being measured within the trials but median OS has not yet been reached which may be reassuring.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not as far as we are aware.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The final analysis within the 3 entrectinib studies has not been published at the time of writing but data are available in abstract form from conference proceedings. We are aware also there may be ongoing analyses looking at real-world data comparators but these data are not available for our review.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA529]?	There has been an update to the PROFILE 1001 data reported in Annals of Oncology: Shaw et al. Ann Oncol Apr 2019. doi: 10.1093/annonc/mdz131. [Epub ahead of print] PMID: 30980071.

21. How do data on real-world experience compare with the trial data?	Relatively few patients will have been treated with crizotinib for ROS1 positive disease since introduction of the technology appraisal due to the low frequency of the alteration. There are, therefore, no significant data to report on real-world experience.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to molecular pre-screening would need to be considered.
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Entrectinib is an effective ROS1 inhibitor with CNS penetration and intracranial activity
- Treatment of brain metastases is a significant unmet need in patients with ROS1 fusion positive lung cancer
- Data for entrectinib appear superior to crizotinib in terms of PFS and intracranial activity (OS data immature for entrectinib)
- Randomised clinical trial data are not available. Comparisons with historical data and real-world data are required
- Pre-screening for ROS1 fusion should be available routinely for all NSCLC (non-squamous) patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 129317

BMJ Technology Assessment Group

Title: Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

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Date completed: 09/08/2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 129317

Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Acknowledgements:
The ERG would like to thank Dr Dionysis Papadatos-Pastos (Consultant in Medical Oncology, University College London Hospitals and The Princess Alexandra Hospital) and Professor Fiona Blackhall (Professor of Thoracic Oncology, University of Manchester and Consultant in Medical Oncology, The Christie Hospital NHS Trust) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Kew KM, Bacelar M, Wakefield V, Cain P. Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report.
Kayleigh Kew	Clinical lead for the critical appraisal of the company's submission and clinical evidence; drafting of the clinical effectiveness sections and summaries.
Victoria Wakefield	Clinical support for the critical appraisal of the company's submission and clinical evidence; drafting of the background and safety sections; reviewing all other clinical sections of the report.
Mariana Bacelar	Economic lead. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Peter Cain	Economic support. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
ACD	Appraisal consultation document
AE	Adverse event
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BoR	Best overall response
CADTH	Canadian Agency for Drugs and Technologies in Health
CBR	Clinical benefit rate
CCOD	Clinical cut-off date
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CQ	Clarification questions
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effect
DLT	Dose-limiting toxicity
DoR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC-QLQ-C30	European Organization for Research and Treatment Quality of Life Core Questionnaire
EORTC-QLQ-LC13	European Organization for Research and Treatment Quality of Life Lung Cancer module
EoT	End of treatment
EQ-5D-3L	EuroQol 5-Dimensions questionnaire with 3 levels
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FAD	Final appraisal determination
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridisation test
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INAHTA	International Network of Agencies for Health Technology Assessment
INV	Investigator-assessed

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility value
HTA	Health technology assessment
KM	Kaplan–Meier
LYG	Life-years gained
MIMS	Monthly Index of Medical Specialities
NIHR	National Institute for Health Research
NTRK	Neurotrophic-tropomyosin receptor kinase
MAIC	Matched-adjusted indirect comparison
MTD	Maximum tolerated dose
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressed disease
PEM+PLAT	Pemetrexed plus platinum chemotherapy
PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria for Solid Tumors
REML	Restricted maximum likelihood estimation
RPSFTM	Rank-preserving structural failure time model
SAE	Serious adverse event
SD	Standard deviation or stable disease (depending on context in report)
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TKI	Tyrosine kinase inhibitor
TNM	Tumour node metastasis system of classification
ToT	Time on treatment
TSD	Technical Support Document
TTD	Time to treatment discontinuation
WTP	Willingness to pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company (Roche) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the safety and effectiveness of entrectinib for patients with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer (hereafter ROS1+ NSCLC). The company provided an overview in their submission of ROS1+ NSCLC including its pathogenesis, staging, incidence, symptoms, prevalence of central nervous system (CNS) metastases and patient prognosis. The evidence review group (ERG) notes that NSCLC driven by ROS1 fusion proteins are rare (1-2% of all NSCLC) and generally occur in adenocarcinoma, the most common form of non-squamous NSCLC. People who present with ROS1+ NSCLC tend to be younger and have light or no smoking history compared to the wider lung cancer population.

Entrectinib is an oral, potent inhibitor of the tyrosine kinases encoded by the ROS1, NTRK1, NTRK2, NTRK3 and ALK genes with activity in the central nervous system (CNS). The anticipated marketing authorisation for entrectinib is [redacted] following confirmation of ROS1+ status, which is anticipated from the European Medicines Agency (EMA) in [redacted] (information provided by the company during the factual accuracy check). The ERG's clinical experts agreed with the company that crizotinib has become the standard first-line treatment for ROS1+ NSCLC since it was recommended via the Cancer Drugs Fund (CDF) in 2018 and is currently the only targeted therapy available for patients with ROS1+ NSCLC. Since the approval of crizotinib, tumour tissue is now tested for ROS1 and other somatic oncogenic drivers as standard when patients are diagnosed with non-squamous NSCLC.

The company propose that entrectinib will be used at first or second line for patients with ROS1+ NSCLC. The ERG's clinical experts agreed that crizotinib is the most relevant comparator and, while the company acknowledge NICE's position regarding comparators funded via the CDF, the company state that they are actively seeking a CDF recommendation for entrectinib. Experts stated that entrectinib will likely displace crizotinib as the preferred first-line treatment should it be recommended because of its proposed benefits for treating and preventing CNS disease. The ERG's clinical experts stated that, for this reason, entrectinib may be offered to patients who progress on crizotinib and agreed that pemetrexed plus platinum therapy (PEM+PLAT) is the relevant comparator for entrectinib in this context. All other comparators listed in the NICE final scope would be used later in the pathway.

The company's clinical evidence is based on two Phase I studies (ALKA; n = 58; Italy, and STARTRK-1; n = 76; USA, South Korea and Spain) and one Phase II study of entrectinib (STARTRK-2; n = 207; Australia, Europe, Asia and the USA). ALKA, STARTRK-1 and STARTRK-2 are all ongoing, single-arm, open-label studies recruiting patients with a range of locally advanced and metastatic solid tumours

testing positive for ROS1, ALK, or NTRK1/2/3 genetic alterations. ALKA, STARTRK-1 and STARTRK-2 have enrolled [redacted] patients with ROS1+ NSCLC, but the company's preferred efficacy set is based on an integrated analysis including 53 patients. The company's primary analyses do not include [redacted] patients who had less than 12 months' follow-up, or [redacted] patients who were enrolled but did not meet the study eligibility criteria regarding prior ROS1-inhibitor therapy, performance status or measurable disease at baseline.

Clinical experts considered patients with ROS1+ NSCLC enrolled in the entrectinib studies relevant to the NICE final scope and representative of patients with ROS1+ NSCLC in the UK (mean age ~53 years, ~60% female, primarily adenocarcinoma histology, ~90% performance status of 0 or 1 and ~40% with a history of smoking, high proportion of brain metastases [44%]). The proportion of Asian patients is higher in the ERG preferred efficacy set (46.2%) than in the company's efficacy set (35.8%), and both are higher than in the UK, but race is not known to affect disease course or response to treatment in ROS1+ NSCLC. Approximately two thirds of patients treated with entrectinib had received at least one prior systemic therapy, some of which are not available in the UK, meaning the effectiveness of entrectinib for untreated ROS1+ NSCLC may be underestimated.

The Phase I studies (ALKA and STARTRK-1) had a primary aim of identifying dose limiting toxicities and the maximum tolerated dose of entrectinib, and so patients received a range of doses and schedules outside the intended marketing authorisation for entrectinib. The company was unable to confirm which patients had received the recommended starting dose of 600 mg, and the ERG, therefore, considers results from STARTRK-2 to be more reliable for decision making within the proposed marketing authorisation. The primary outcome of STARTRK-2 was objective response rate (ORR) as assessed by blinded independent central review (BICR), and secondary outcomes included overall survival (OS), progression-free survival (PFS; BICR and investigator assessed), measures of health-related quality of life (HRQoL), intracranial response and PFS, and safety.

The entrectinib studies provide no comparative data and so systematic literature reviews (SLRs) were carried out to identify studies to support matching adjusted indirect comparisons (MAICs) of entrectinib versus crizotinib and PEM+PLAT. The company took an 'all lines' approach for the MAICs because most patients with ROS1+ NSCLC in the entrectinib studies had received prior systemic therapy and the population was too small to support separate analyses by line of treatment. Comparison with crizotinib in the correct ROS1+ NSCLC population was possible via an unanchored MAIC with another single-arm study (PROFILE 1001), but the comparison with PEM+PLAT incorporated evidence and had to make additional assumptions from studies of ALK+ NSCLC (ASCEND-4 and PROFILE 1014).

Data were submitted for all outcomes listed in the NICE final scope, although time to treatment discontinuation (TTD) was only addressed in the cost-effectiveness section of the submission. The

MAICs considered OS, PFS, ORR and discontinuation due to adverse events (AEs), and only OS and PFS are reflected in the economic model.

1.2 Summary and critique of the clinical effectiveness evidence

1.2.1 Evidence supporting entrectinib for patients with ROS1+ NSCLC

The ERG disagrees with the efficacy set used for the company's primary analysis and defined a preferred efficacy set which includes 78 patients with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline from STARTRK-2 with no minimum follow-up. STARTRK-2 is the only study to deliver entrectinib in line with its proposed marketing authorisation and assess tumour scans prospectively. The ERG accepts that removing the minimum follow-up restriction means that DoR is likely to be more stable in the company's preferred analysis but considers the ERG's analysis preferable for the efficacy outcomes reflected in the economic model (OS and PFS) because patients with shorter follow-up contribute useful data for OS and PFS up to the point at which they are censored.

The primary outcome of ORR (BICR) in the company's primary integrated analysis of ALKA, STARTRK-1 and STARTRK-2 (clinical cut-off date [CCOD] 31 May 2018) was [redacted] ([redacted] complete and [redacted] partial response) and median DoR was [redacted] ([redacted] months, 95% CI: [redacted]). Median OS was not estimable in the company's primary analysis (median follow-up 15.5 months; [redacted] deaths [[redacted]]) and median PFS was [redacted] months (95% CI: [redacted] months).

In the ERG's preferred analysis including 78 patients from STARTRK-2 who all received the recommended 600 mg dose of entrectinib, ORR by BICR was slightly [redacted] at [redacted] and median DoR was [redacted] ([redacted] months; 95% CI [redacted]). There were more deaths in the ERG's preferred analysis and median OS was [redacted] months (mean follow-up 13.3 months; [redacted] deaths[[redacted]]), but the data are still immature and so the median is unreliable. Median PFS using the ERG's preferred efficacy set was [redacted] than the company's analysis at [redacted] months (95% CI [redacted]).

Intracranial outcomes were not listed in the NICE final scope, but single-arm results presented in the submission provide some support for the proposed activity of entrectinib for CNS disease. The ERG's clinical experts expressed the need for CNS-active treatments because brain metastases are common with ROS1+ NSCLC and have a profound impact on prognosis and quality of life. Intracranial outcomes were not analysed in the MAICs conducted to compare entrectinib with crizotinib or PEM+PLAT and are not reflected in the economic model.

HRQoL data for entrectinib were collected in STARTRK-2 and suggest patients in the company's and the ERG's preferred efficacy sets had moderate-to-high functioning and moderate lung cancer symptom burden at baseline. While the company highlights particular time points where some scores peaked (e.g. improvement in severe cough after the first dose) the ERG considers there to be some indication of

deterioration in global health status, functioning and symptom domains of the EORTC QLQ-C30 between baseline and the end of treatment. Symptom burden scores were relatively stable on the EORTC LC-13, with only dyspnoea showing a clear sign of worsening, but variation between means and medians in each efficacy set and large standard deviations and ranges suggest a great deal of variation within the population.

Safety analysis were conducted on a wider population than the efficacy sets, including all ROS1+ NSCLC patients who received at least one dose of entrectinib in ALKA, STARTRK-1 and STARTRK-2 irrespective of prior ROS1-inihibitor therapy, measurable disease at baseline, dose or follow-up ([redacted]). [redacted] of patients experienced at least one AE and [redacted] of patients were deemed to have a treatment-related AE. Treatment-related Grade 3 or higher AEs occurred in [redacted] of the ROS1+ patients and treatment-related SAEs in [redacted]% of patients. The most frequently reported treatment related AEs in the ROS1+ population were dysgeusia ([redacted]%), dizziness ([redacted]%), constipation ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), and fatigue ([redacted]%). AEs led to dose interruption in [redacted] and dose reduction in [redacted] of ROS1+ patients..

A subgroup analysis in line with the NICE final scope suggests that PFS is likely to be [redacted] and response rates [redacted] for patients with CNS disease than those without CNS disease at baseline, but formal significance tests were not performed. Differences in PFS and DoR for patients with and without CNS disease at baseline were far more pronounced in the company's preferred analysis (PFS [redacted] versus [redacted] months; DoR [redacted] versus [redacted] months) than ERG's preferred analysis. All subgroup analyses are based on small numbers of events, particularly for OS.

A *post hoc* subgroup analysis requested by the ERG does not suggest prior TKI use is an important effect modifier for OS, PFS and ORR, but the ERG notes that patients who had received a prior ROS1-targeted TKI and were excluded from the company's and the ERG's preferred efficacy sets, which the clinical experts considered appropriate. Further prespecified subgroup analyses for the primary outcome of ORR showed rated of [redacted] to [redacted] across subgroups for entrectinib dose (below 600 mg, 600 mg and above 600 mg), ECOG performance status (0, 1, 2, ≥3), and a range of subgroups to explore type and number of prior anticancer therapies (systemic, chemotherapy, targeted, hormonal, radiation, surgery and brain radiation). The ERG does not consider there to be a sufficient number of patients to draw any meaningful conclusions about subgroup differences.

1.2.2 Indirect treatment comparisons

PROFILE 1001 – a multicentre Phase I single-arm study of crizotinib for ROS1+ NSCLC (n = 53) – was chosen to inform an MAIC of entrectinib versus crizotinib. The ERG notes the following with regard to the MAIC based on PROFILE 1001:

- While it does not provide comparative data, the ERG's clinical experts agree that PROFILE 1001 is the most robust evidence for crizotinib in a ROS1+ NSCLC population.

- Like the entrectinib studies, PROFILE 1001 included a mixed population of treatment-naïve and pre-treated patients and the primary outcome was ORR by IRR.

- The company and ERG preferred efficacy sets for entrectinib were reweighted to match PROFILE 1001 for sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, prior treatments (treatment naïve vs prior treatment), and age.

ASCEND-4 – a large, multicentre, Phase III RCT of ceritinib versus PEM+PLAT (with pemetrexed maintenance therapy) for untreated ALK+ NSCLC (n = 187 in the PEM+PLAT group) – was chosen to inform an MAIC of entrectinib versus PEM+PLAT because there were no studies in an ROS1+ NSCLC. The ERG notes the following with regard to the MAIC based on ASCEND-4:

- ASCEND-4 is a well conducted RCT and, while other ALK+ NSCLC studies were identified that include a PEM+PLAT arm, ASCEND-4 is the only study to give pemetrexed maintenance therapy as is done in UK clinical practice.

- The ERG considers there to be no consensus about the appropriateness of using evidence from ALK+ NSCLC as a proxy for ROS1+ NSCLC, and there is no way to quantify and, if neccssary, adjust for differences in treatment effect that are attributable to the underlying gene fusion.

- At the time of analysis, 42.7% of patients who received PEM+PLAT (80/187) had crossed over to receive ceritinib, and 51.6% had received any subsequent ALK inhibitor (105/187),[70] so the survival benefit of PEM+PLAT is potentially overestimated.

- The study recruited only patients with untreated disease which could not be adjusted for because most patients in the entrectinib studies had received prior systemic therapies. However, the company's and the ERG's preferred efficacy sets for entrectinib were reweighted to match ASCEND-4 for sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, age, and disease stage (stage IIIB vs stage IV non-CNS metastasis vs stage IV CNS metastasis).

The company use an alternative method to derive estimates of OS and PFS for PEM+PLAT in the economic model using PROFILE 1014 and present the results of the ASCEND-4 MAIC as a scenario analysis. The ERG considers there to be important limitations of both methods used to derive estimates for PEM+PLAT but considers the estimates of ASCEND-4 more clinically plausible (see economic issues).

The company's MAIC based on PROFILE 1001 suggests that entrectinib has benefits over crizotinib for OS ( ) and ORR ( ), but the treatments may offer similar PFS ( ). The ERG's preferred MAIC using PROFILE 1001 suggests a OS benefit of entrectinib compared with crizotinib ( ) than the MAIC using the company's preferences. The ERG's results also show different effects to the company's for ORR and PFS, with the ERG's preferred MAIC suggesting in ORR between the treatments ( ) and a trend towards of crizotinib over entrectinib for PFS . A sensitivity analysis using PFS INV data from the entrectinib studies was favourable to crizotinib than the BICR analysis using the ERG's preferences ( ), and the company's ( ).

The company's MAIC based on ASCEND-4 suggests that entrectinib also has statistically significant benefits over PEM+PLAT for OS ( ), PFS ( ) and ORR ( ). Results from the ERG's preferred MAIC similarly favour entrectinib, but the benefits are than the company's preferred MAIC for OS ( ), PFS and ORR ( ). The ORR in each analysis shows that the proportion of patients (reweighted) responding in the ERG's preferred efficacy set for entrectinib is somewhat than the company's primary efficacy set ( ), but both are than the 26.7% ORR for PEM+PLAT.

After reweighting, both MAICs suggest that a similar proportion of patients discontinue entrectinib due to AEs as crizotinib (vs 7.54%) and PEM+PLAT (vs 8.56%), based on the wider ROS1+ NSCLC safety population for entrectinib. AEs in the economic model are based on naïve comparisons.

1.3 ERG commentary on the robustness of evidence submitted by the company

1.3.1 Strengths

- Patients with ROS1+ NSCLC in the submitted studies of entrectinib are considered generally reflective of patients with ROS1+ NSCLC in the UK.

- The company provided full results for the ERG's preferred efficacy set, including alternative MAICs to compare entrectinib with crizotinib and PEM+PLAT.

- Methods used for the MAICs were mostly in line with guidance from the Decision Support Unit and justification was provided where the limits of the evidence base prevented all effect modifiers being included as covariates.

- Blinded assessments of ORR and PFS were used and sensitivity analyses were conducted to explore the robustness of results to the method of assessment.

- Subgroup results were available, or provided at the clarification stage, to assess the impact of baseline CNS metastases and prior TKI use.

- The formulae within the economic model are generally sound and the economic model is well constructed.

1.3.2 Weaknesses and areas of uncertainty

Clinical

Evidence for entrectinib is limited to three ongoing, open-label, single-arm, mixed population studies which have so far enrolled [redacted] patients with ROS1+ NSCLC, and a much smaller number were included in the company's primary efficacy analyses (n = 53). Evidence for crizotinib in ROS1+ NSCLC – which the ERG agrees is the most relevant comparator despite only being available through the CDF – is also limited to a single-arm study and observational data, and there are no directly relevant data for PEM+PLAT.

Dose could not be confirmed for the Phase I studies, and so the ERG defined a preferred efficacy set which includes 78 patients who met the study eligibility criteria for STARTRK-2 (ROS1-inhibitor naïve, measurable disease at baseline), because it was the only study to deliver entrectinib in line with its proposed marketing authorisation.

Data were not available for PROFILE 1001 to match the entrectinib population by disease stage and presence of CNS metastases which are known to impact survival. The MAIC based on PROFILE 1001 is unanchored and so results for the crizotinib MAIC could be confounded by these and other unknown differences between the populations.

The ERG considers there to be important limitations of both methods used to derive estimates for PEM+PLAT using studies of ALK+ NSCLC (ASCEND-4 or PROFILE 1014) but considers those related to PROFILE 1014 more serious. The ERG found no consensus about the appropriateness of using evidence from ALK+ NSCLC as a proxy for ROS1+ NSCLC, and there is no way to quantify or adjust for differences in absolute or relative treatment effects that are attributable to the underlying gene fusion. The appraisal committee for TA529 (crizotinib for ROS1+ NSCLC) considered the use of evidence for ALK+ NSCLC, "very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals."

The unanchored MAIC with the PEM+PLAT group of ASCEND-4 (company scenario analysis and ERG base case) potentially underestimates the OS benefit of entrectinib versus PEM+PLAT because 42.7% of the PEM+PLAT group in ASCEND-4 crossed over to receive ceritinib after PEM+PLAT (and 105/187 [56.1%] had received any ALK inhibitor), whereas patients generally receive targeted treatments prior to PEM+PLAT in UK clinical practice. The ERG had serious concerns with the method using PROFILE 1014 which are discussed in the economic section.

The OS KM curves for comparing entrectinib and crizotinib are likely to be unreliable from approximately 20 months due to the level of censoring required (and 69.8% for entrectinib and crizotinib in the company's MAIC and and 49.1% in the ERG's preferred MAIC using updated results for PROFILE 1001), which introduces substantial uncertainty in the extrapolation required for the economic model. Moreover, OS observed in studies of ROS1+ NSCLC, including those used for the MAICs, is much longer than has been achieved in clinical practice (51.4 months for crizotinib in PROFILE 1001 versus 18.5 months in the Flatiron registry), so the results may not reflect the effectiveness that might be expected for patients treated in the NHS.

Economic

The ERG's main concerns are related to the immaturity of OS data in the single-arm STARTRK-2 study, and the results of both the OS and PFS MAICs comparing entrectinib with crizotinib, which have shown non-statistically significant results. The ERG is concerned that survival with entrectinib is considerably overestimated in the economic analysis (using the ERG's preferred efficacy set and even more markedly with the company's data set).

The key issues related with the analysis comparing entrectinib with crizotinib are summarised below in detail:

1. There is an apparent disconnection between PFS and OS gains for entrectinib. The results of the updated MAIC show that entrectinib is not statistically significantly different from crizotinib in delaying patients' progression – the trend in the KM curves suggests that patients on entrectinib progress faster than patients on crizotinib. Using the ERG's preferred efficacy set, comparing post-progression survival (PPS) for treatment with entrectinib (months) and crizotinib (18.48 months), entrectinib yields a -month additional PPS gain. This compares with a PFS "loss" of months for entrectinib patients (months for entrectinib vs 23.6 months for crizotinib), suggesting that the treatment benefit with entrectinib only happens after progression (and after patients have stopped treatment) despite patients progressing quicker on entrectinib.

   This discrepancy is even more accentuated in the company's base case analysis (using the company's preferred analysis set), where the PPS gain with entrectinib is months, compared

with a PFS "loss" of [redacted] months. These estimates suggest a 3-year survival gain with entrectinib compared with crizotinib, derived only after patients progressed quicker (or arguably at the same time) as crizotinib patients.

Overall, the ERG considers the absolute PFS and OS gains with entrectinib in the company's base case analysis to be clinically implausible, with an overall survival of 7.5 years for entrectinib patients. Nonetheless, it is likely that the crizotinib curves are also overestimated compared with UK clinical practice, as per clinical expert opinion provided to the ERG. From an incremental perspective (i.e. PFS and OS gains), the ERG also considers the company's base case analysis to produce unsubstantiated results compared to crizotinib.

The ERG highlights that a less extreme, but comparable, situation was reported in TA529 around the relationship between the PFS and PPS gains between crizotinib and PEM+PLAT. The ERG in TA529 mentioned an analysis undertaken by the FDA, which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib), suggesting that it is not unreasonable to assume similarity between PFS and OS treatment effects (in terms of additional months spent in these states) in the absence of other evidence.

Therefore, in order to explore some of the uncertainty around the OS benefits for entrectinib vs crizotinib, the ERG's base case assumes a PFS HR=1 and an OS HR =1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression and extending life. The ERG has not heard from its clinical experts that the PFS results favouring crizotinib vs entrectinib are expected in clinical practice, and so these could potentially be attributable to the inaccuracy of the MAIC results due to low statistical power or unadjusted for confounding factors.

Clinical expert opinion sought by the ERG supported the anticipated benefit of entrectinib on delaying CNS progression when compared with crizotinib, however, there are few data to corroborate this CNS advantage over crizotinib, and how this translates into overall disease progression and ultimately survival.

In light of the weak and uncertain evidence underpinning the relative treatment effect of entrectinib compared with crizotinib, the ERG is concerned with the fact that entrectinib, if recommended, is likely to displace crizotinib as a first-line treatment for ROS1+ NSCLC and that clinicians are unlikely to give second-line crizotinib after patients have received entrectinib.

Given the ERG's assumption of equal PFS and OS for both treatments, the ERG's base case economic analysis for entrectinib vs crizotinib is reduced to a cost comparison analysis. The total crizotinib costs in the ERG's preferred analysis amount to £118,912 while the total costs for entrectinib amount to [redacted]. With this difference in costs, crizotinib's list price would have to

be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (i.e. [redacted]). If the total costs associated with crizotinib were lower than [redacted] then the ICER for entrectinib vs crizotinib would increase as the total costs for crizotinib decrease.

Regarding the analysis of entrectinib vs PEM+PLAT, the ERG's concerns with the uncertainty in the entrectinib data remain, however, there seems to be a more plausible relationship between PFS and OS outcomes for entrectinib vs PEM+PLAT, particularly when the ASCEND-4 MAIC results are used to estimate survival with PEM+PLAT (instead of the company's base case approach using PROFILE 1014). Entrectinib shows a statistically significant advantage over PEM+PLAT in delaying patients' disease progression and a non-significant, albeit positive trend, in OS.

The key issues related with the analysis comparing entrectinib with PEM+PLAT are summarised below in detail:

1. In the base case analysis, OS and PFS for PEM+PLAT were estimated by applying the published OS and PFS HRs from PROFILE 1014 to the crizotinib arm of the model. As an alternative scenario, the company ran an MAIC using STARTRK-2 entrectinib data for the ERG's preferred efficacy set and the chemotherapy arm in the ASCEND-4 trial. The inverse of the estimated HRs from the MAIC were then applied to the modelled entrectinib OS and PFS curves.

   The company reported that the PROFILE 1014 OS and PFS HRs were previously used and accepted for ROS1+ NSCLC patients in TA529. Upon inspection of TA529 documents, the ERG concluded that the use of HRs from PROFILE 1014 was not accepted by the TA529 committee. The FAD for TA529 stated that, "*The committee noted the ERG's comments that in both trials* [PROFILE 1014 was one of them]*, the proportional hazards assumption* […] *was not valid for progression-free survival so any hazard ratios for progression-free survival should be interpreted with caution. The ERG also highlighted that the overall survival estimates were unreliable because of high rates of crossover, and that statistical methods for adjustment were not reported transparently. The committee agreed that the results showed crizotinib to be more effective than chemotherapy for ALK-positive NSCLC, but that its relative effectiveness in ROS1-positive advanced NSCLC remained uncertain."*

   Therefore, the ERG disagrees with the company's conclusion that the PROFILE 1014 HRs were accepted by the TA529 committee (particularly regarding the concerns around the OS HR). Another limitation, that was acknowledged by the company, of using the PROFILE 1014 OS HR is that the trial did not include subsequent maintenance treatment with pemetrexed, which the ERG's clinical experts indicated is part of routine clinical practice in the NHS, thus potentially underestimating the effect of pemetrexed compared with current practice.

The ERG has several concerns with the company's use of the RPSFTM-adjusted OS HRs from the latest data cut-off from PROFILE 1014. The ERG report in TA529 stated (in reference to PROFILE 1014) that, "*…the company's RPSFTM method of adjusting for the impact of treatment switching is flawed and that, as such, the company's crossover-adjusted HR is unreliable.* […] *the ERG is also unsure whether the RPSFTM method is appropriate for adjusting for crossover, since the RPSFTM, and indeed the IPE, assumes a "common treatment effect", i.e., that the treatment effect received by patients who switch must be the same as the treatment effect received by patients initially randomised to the experimental group. The ERG notes that it is unclear whether this assumption would hold since patients randomised to pemetrexed+platinum who switch to crizotinib may, at that time, have more advanced disease than patients who were originally randomised to crizotinib; the patients randomised to pemetrexed+platinum, therefore may not have the same capacity to benefit from crizotinib treatment following disease progression as patients randomised to crizotinib. The ERG recognises that it is not possible to test the "common treatment effect" assumption, and that, in practice, this assumption is highly unlikely to ever be exactly true."* The ERG report in TA529 concludes that, "*In summary, the ERG considers that there is no method of adjusting for treatment switching that the ERG can confidently conclude would generate unbiased OS risk estimates for crizotinib versus chemotherapy for patients in the PROFILE 1014 trial.* [and that] *The ERG prefers to accept the level of crossover (19.2%) rather than use the company's RPSFTM-adjusted curve, as the company's RPSFTM-adjusted curve for treatment with crizotinib in the first-line model estimates better survival for crizotinib than the unadjusted curve. The ERG has not seen the details of the company's crossover methods and therefore cannot comment on the approach."*

At the time of TA529, the PROFILE 1014 OS data were more immature than the crizotinib data used by the company in the entrectinib submission. Therefore, while the ERG in TA529 preferred to accept the level of cross-over of 19.2% of patients and use the unadjusted OS data, the updated PROFILE 1014 data is based on 84% of patients crossing over from PEM+PLAT to crizotinib.

The OS HRs from PROFILE 1014 are marked confidential in TA529, and the ERG could not find the unadjusted OS HR in any published papers based on the earliest data cut for the trial. Furthermore, the latest PROFILE 1014 OS publication reports an unadjusted HR of 0.760 (95% CI: 0.548 to 1.053), which compares to the adjusted HR of 0.346 (95% CI: 0.081 to 0.718). However, the proportion of patients crossed over at the latest data cut-off reached 84% and so the ERG does not consider that the use of the unadjusted HR is a robust option.

Even though the ERG agrees with the company that the assumptions associated with the base case approach are less strong than those required for the unanchored ASCEND-4 MAIC (because the former retains the benefits of a randomisation, and only assumes that the relative effect of crizotinib

versus PEM+PLAT is similar for ALK+ and ROS1+ NSCLC populations), there is considerable uncertainty around either approach. Furthermore, ASCEND-4 included maintenance treatment with pemetrexed.

In summary, the ERG considers that both approaches presented by the company to estimate OS for PEM+PLAT have considerable flaws. Nonetheless, given the conclusions in TA529 that the maximum expected survival benefit of crizotinib vs PEM+PLAT would be between 13 and 16 months; and that the model results using the PROFILE 1014 HR in the ERG's preferred efficacy set yields a survival benefit of 27.5 months for crizotinib and using the ASCEND-4 MAIC HR produces a survival benefit of 3.9 months, the ERG considers that using the ASCEND-4 MAIC produces more conservative results.

2. A key driver of the economic results for entrectinib vs PEM+PLAT is the assumption made for the duration of maintenance treatment with pemetrexed. The ERG's base case ICER drops from £45,629 to £22,821 when it is assumed that maintenance treatment is given until progression (mean time to progression is 11.43 months in the ERG's base case). If, for example, maintenance treatment is assumed to be given for 6 cycles (as the clinical experts indicated to the ERG that this is a plausible median duration), the ERG's ICER increases to £35,975 per QALY gained. Therefore, the ERG notes the importance of considering the clinical plausibility of this parameter.

   The ERG notes that TA529 used time to treatment discontinuation (TTD) data from PROFILE 1014 to estimate treatment duration with PEM+PLAT and did not use the 4 to 6 cycles assumption as suggested by the company.

The ERG also has some concerns common to the analyses of entrectinib vs crizotinib and entrectinib vs PEM+PLAT. These consist of:

1. The analysis of STARTRK-2 utility data – the company provided very little detail in the CS to describe their approach to the analysis. In response to clarification questions, the company provided the coefficients of each variable at each stage of the selection procedure for the mixed regression model but did not provide p-values to show how robust each estimate was for each stage. The ERG considers that given the limited data even in the ERG's preferred efficacy set, it is unlikely for any of the coefficients to be significant at the default significance thresholds, so the exclusion of all fixed effects is not unexpected. However, the ERG would have liked to see how close these p-values were to the thresholds for inclusion.

   The company applied a restricted maximum likelihood estimation (REML) approach to the mixed model. This means the mixed model was fitted in a two-stage approach in which only the random-effects were included in the model initially, and then the fixed effects were included on

top of the resulting random effects model to account for the remaining variance not explained by the random effects. The ERG considers that from a methodological point of view the company's approach is reasonable, however, it is concerned that the company have not implemented the results of the regression model correctly. The resulting model includes only random effects for time from first assessment and for the intercept, as all fixed effects had p-values greater than 0.05 and were therefore excluded. To implement the company's final random-effects regression model requires a coefficient for the time from first assessment as well as a value for the intercept; neither of these values appear to have been provided by the company. The standard summary output of this regression model in R does not provide estimates of the random-effects coefficients as there is an estimate for each individual in the dataset. Therefore, the mean of these estimates needs to be calculated and those values should be used to calculate the HSUV inputted into the economic model.

Further to this, the ERG is unclear why the company chose the 0.73 utility value as this was the fixed effect intercept that was estimated as part of the selection procedure in the second stage of the regression model, where all fixed effects were excluded in the selection procedure. The company's estimate of the HSUV for the PFS health state is therefore flawed, and the ERG disagrees with its use in the economic analysis.

Furthermore, the ERG considers it a potentially serious limitation to use different data sources to inform different health states in the economic model, as there is a correlation between health state values that is lost with this approach, and the relationship between the values of each health state are likely to be a more influential driver in the economic model than the baseline utility scores. Therefore, the ERG used the utility values accepted in TA529 (PFS=0.81; PPS=0.66), as it considers the company's base case approach flawed and the unadjusted raw data less robust than the data previously accepted by the committee for TA529.

1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG

The exploratory analyses presented by the ERG are based on the ERG's preferred efficacy set for entrectinib and the updated PROFILE 1001 data. Table A reports results for entrectinib vs PEM+PLAT while Table B reports results for entrectinib vs crizotinib. The analyses consist on the following:

1. The ERG ran a scenario analysis to assess the impact of using a Weibull distribution to fit PFS data for entrectinib in the model;

2. The ERG ran a scenario analysis using a Weibull curve to fit ToT in the economic model;

3. The ERG conducted sensitivity analysis assuming a PFS HR=1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression;

4. The ERG conducted sensitivity analysis assuming an OS HR=1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in extending life;

5. The ERG ran a scenario analysis using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS;

6. The ERG assumed that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments (however this approach needs to be caveated by the fact that it illustrates a cost scenario disconnected with the underlying trial data at least for entrectinib);

7. The ERG tested the impact of the clinical expert's suggested resource for the PFS and PPS health states. The key changes were to remove the use of chest X-rays and increase the proportion of patients who would receive CT scans. Also, the frequency of GP visits and cancer nurse visits in the PFS health state was reduced;

8. The ERG has tested the impact of applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib (a scenario analysis provided by the company during clarification);

9. The ERG conducted assessed the impact changing the prevalence of ROS1+ from 1.69% to:

    a. 1%;

    b. 0.5%;

10. Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using:

    a. The company's base case effectiveness assumption for PEM+PLAT (estimated with the PROFILE 1014 HR);

    b. The alternative effectiveness assumption for PEM+PLAT (estimated with the ASCEND-4 MAIC);

11. Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT. To note is that this scenario also changes the duration of treatment with PEM+PLAT from 6 to 4 cycles in the model, to match the duration of treatment with PEM+PLAT in ASCEND-4.

Results from the ERG's scenario analysis show that for the comparison of entrectinib with PEM+PLAT the key model driver is the source of effectiveness chosen to estimate OS and PFS for PEM+PLAT, with the ICER increasing from £21,845 to £52,399 per QALY gained when treatment effectiveness is estimated with the ASCEND-4 MAIC HR instead of the PROFILE 1014 HR. This increase is due to a much smaller survival gain for entrectinib when PEM+PLAT is estimated using ASCEND-4 rather than PROFILE 1014. Equally important in driving the model results is the assumption around the duration of maintenance treatment with pemetrexed, as it considerably increases treatment costs for the comparator in the company's base case assumptions. However, when combined with the scenario analysis assuming that all entrectinib patients receive PEM+PLAT as a subsequent treatment, the impact of the duration of maintenance treatment on the ICER is reduced. To note is that the company assumed a maximum treatment duration of 8 months for maintenance treatment with pemetrexed when given as a subsequent treatment.

As the prevalence of ROS1+ decreases, the cost for identifying a true-positive patient increases. However, the ERG notes that in the comparison of entrectinib with crizotinib, these costs cancel out as patients assigned to first-line treatment would have to be tested regardless of receiving one treatment or the other. For the comparison of entrectinib vs PEM+PLAT, the ERG finds the inclusion of ROS1+ fusion testing somewhat meaningless as this is a relevant treatment comparison only for second-line treatment, at which point this test would have already occurred.

Using the raw mean utilities from STARTRK-2 ([redacted] for PFS and [redacted] for PPS) decreases the ICER from £21,845 to £19,940 as the QALY loss associated with progressing increases (i.e. the difference in values is bigger) compared to the company's base case estimates.

Finally, it should be noted that assumptions around the ToT for entrectinib and the OS HR for entrectinib vs crizotinib also drive the PEM+PLAT comparison results. This is because the PEM+PLAT OS and PFS curves are estimated (in the company's base case approach) by applying the PROFILE 1014 HR to the crizotinib OS and PFS curves, respectively.

All the scenario analyses undertaken for the comparison of entrectinib with crizotinib produced dominant ICERs for entrectinib, with the exception of assuming no survival benefit between entrectinib and crizotinib. In the latter scenario the ICER amounts to £3,341,867 per QALY gained for crizotinib vs entrectinib, as the company's PFS MAIC resulted in favourable results for crizotinib (i.e. patients progress faster on entrectinib than on crizotinib). Thus, if no survival gain is assumed to "compensate" for the negative PFS impact, patients accrue less QALYs on entrectinib than on crizotinib albeit at a lower cost. Nonetheless, the ERG reiterates its concerns that the analysis based on crizotinib's list price is meaningless, as crizotinib is currently available in the CDF with a confidential discount.

Table A. Results of the ERG's scenario analysis for entrectinib vs PEM+PLAT

Analysis from list	Results per patient	Entrectinib (1)	PEM+PLAT (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,845**	
1	**Using a Weibull distribution to fit PFS**			
	Total costs (£)	[redacted]	20,422	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,835**	
2	**Using a Weibull distribution to fit ToT data for entrectinib in the model**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£24,366**	
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	20,464	[redacted]
	QALYs	[redacted]	0.86	[redacted]
	ICER		**£21,736**	
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	21,507	[redacted]
	QALYs	[redacted]	1.10	[redacted]
	ICER		**£24,216**	
5	**Using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.96	[redacted]
	ICER		**£19,940**	
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	21,662	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,796**	
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS sates**			
	Total costs (£)	[redacted]	21,299	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£22,812**	
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£22,530**	
9a	**Changing the prevalence of ROS1+ from 1.69% to 1%;**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]

	ICER		**£23,380**	
9b	**Changing the prevalence of ROS1+ from 1.69% to 0.5%;**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£27,142**	
10a	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using the company's base case effectiveness assumption for PEM+PLAT (estimated with the PROFILE 1014 HR)**			
	Total costs (£)	[redacted]	35,801	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£13,653**	
10b	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using the company's base case effectiveness assumption for PEM+PLAT (estimated with the ASCEND-4 MAIC)**			
	Total costs (£)	[redacted]	39,889	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER		**£27,940**	
11	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of treatment with PEM+PLAT from 6 to 4 cycles to match the duration of treatment with PEM+PLAT in ASCEND-4**			
	Total costs (£)	[redacted]	21,095	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER		**£52,399**	

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Table B. Results of the ERG's scenario analysis for entrectinib vs crizotinib

Analysis from list	Results per patient	Entrectinib (1)	crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER		**Entrectinib is dominant**	
1	**Using a Weibull distribution to fit PFS data for entrectinib in the model**			
	Total costs (£)	[redacted]	131,011	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER		**Entrectinib is dominant**	
2	**Using a Weibull distribution to fit ToT data for entrectinib in the model**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER		**Entrectinib is dominant**	
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	112,864	[redacted]
	QALYs	[redacted]	2.20	[redacted]
	ICER		**Entrectinib is dominant**	
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			

	Total costs (£)	[redacted]	131,065	[redacted]
	QALYs	[redacted]	2.77	[redacted]
	ICER	**£3,341,867**		
5	**Using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.43	[redacted]
	ICER	**Entrectinib is dominant**		
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	129,560	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS states**			
	Total costs (£)	[redacted]	131,040	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	129,665	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

1.5 ERG base case ICER

The assumptions incorporated in the ICERs presented in Table C (entrectinib vs PEM+PLAT) include the cumulative impact of some of the scenario analyses numbered and described in Section 1.6. The ERG caveats the analyses presented with the high degree of uncertainty embedded in the MAICs undertaken to generate relative treatment effectiveness estimates in the model and the single-arm, immature STARTTRK-2 data available for entrectinib.

The final cumulative ICER for entrectinib vs PEM+PLAT amounts to £22,821 per QALY gained. However, this ICER is highly dependent on the assumption made for duration of maintenance treatment with pemetrexed. The ERG's base case ICER drops from £45,629 to £22,821, when it is assumed that maintenance treatment is given until progression. If, for example, maintenance treatment is assumed to be given for 6 cycles (as the clinical experts indicated to the ERG that this is a clinically plausible median duration), the ERG's ICER is £35,975 per QALY gained.

In ASCEND-4, maintenance treatment with pemetrexed was given every 21-days, until disease progression. Median PFS in ASCEND-4 was 8.1 months (mean not available in the publication), which amounts to 12 cycles of 21-days treatment cycles. Given that patients received 4 initial cycles of

PEM+PLAT, that leaves 8 cycles of maintenance treatment with pemetrexed. Assuming 8 cycles of maintenance treatment in the ERG's base case model results in a £34,000 per QALYs gained. The ERG notes that this ICER corresponds with aligning the treatment effectiveness of PEM+PLAT in the ERG's base case with the respective costs in the underlying ASCEND-4 study.

The ERG ran PSA for its preferred ICER for entrectinib vs PEM+PLAT. The resulting ICER amounts to £25,262 per QALY gained (as compared with the deterministic ICER of £22,821).

Given the ERG's assumption of equal effectiveness for entrectinib and crizotinib in terms of progression and survival, presenting an ICER comparing these treatments is no longer meaningful as the QALY gain in the analysis is zero. The only scenarios relevant in this comparison (i.e. affecting the costs of either entrectinib or crizotinib) is therefore: assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments; and that all patients who progress on entrectinib or crizotinib receive PEM+PLAT as a subsequent treatment.

The total crizotinib costs in the ERG's preferred analysis amount to £118,912, while the total costs for entrectinib amount to [redacted]. With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (i.e. [redacted]). If the total costs associated with crizotinib were lower than [redacted] then the ICER for entrectinib vs crizotinib would increase as the total costs for crizotinib decrease.

Table C. ERG's base case ICERs for entrectinib vs PEM+PLAT

Analysis from list	Results per patient	Entrectinib (1)	PEM+PLAT (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,845**	
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	20,464	[redacted]
	QALYs	[redacted]	0.86	[redacted]
	ICER with all changes incorporated		**£21,736**	
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	21,493	[redacted]
	QALYs	[redacted]	1.09	[redacted]
	ICER with all changes incorporated		**£24,083**	
-	**Using the TA529-accepted utility values of of 0.81 for PFS and 0.66 for PPS**			
	Total costs (£)	[redacted]	21,493	[redacted]
	QALYs	[redacted]	1.15	[redacted]

	ICER with all changes incorporated	**£23,172**		
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	24,388	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£22,130**		
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS sates**			
	Total costs (£)	[redacted]	25,431	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£23,058**		
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	25,431	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£23,164**		
11	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of treatment with PEM+PLAT from 6 to 4 cycles to match the duration of treatment with PEM+PLAT in ASCEND-4**			
	Total costs (£)	[redacted]	27,682	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER with all changes incorporated	**£45,629**		
10b	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years)**			
	Total costs (£)	[redacted]	46,475	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER	**£22,821**		

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The company provided an overview of non-squamous non-small-cell lung cancer (NSCLC) and ROS1 fusion-positive (ROS1+) NSCLC in Section B.1.3 of the company's submission (CS) including: pathogenesis, staging, incidence and prevalence, symptoms, central nervous system (CNS) metastases and prognosis. The final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) defines the population of interest as people with ROS1+ locally advanced or metastatic NSCLC, [redacted].[1]

The Evidence Review Group (ERG) considers the overview of ROS1+ NSCLC presented by the company appropriate and relevant to the decision problem. A synopsis is provided below with supplementary information from the ERG's clinical experts to aid the Committee:

- Lung cancer is the third most common cancer in the UK, accounting for 13% of all cancer cases,[2] with 39,001 cases reported in England and Wales in 2016.[3] Most lung cancers are NSCLC (88.5% in England and Wales in 2016),[3] which can be squamous or non-squamous, an adenocarcinoma is the most common subtype of non-squamous NSCLC.[4]

- Tobacco smoking is the leading cause of lung cancer, but a range of somatic genetic alterations (termed oncogenic driver mutations) including anaplastic lymphoma kinase (ALK) fusions, epidermal growth factor receptor (EGFR) mutations, and ROS1 fusions are more commonly associated with lung cancer in light or non-smokers;

- The identification of somatic oncogenic drivers has led to the development and approval of targeted therapies that inhibit the constitutively activated pathway[5, 6] and the routine inclusion of genomic testing of non-squamous NSCLC tissue. ROS1 testing was included in the 2019/2020 National Genomic Test Directory for Cancer and has now become a standard part of the diagnostic work-up in NSCLC.[7]

- Rearrangements of the ROS1 gene, first reported in NSCLC in 2007, [8] create gene fusions that result in a fusion protein which is constitutively 'switched on', causing cell proliferation in a variety of human cancers (including glioblastoma, NSCLC and ovarian cancer).[9] Known ROS1 fusion partners in lung cancer include FIG, SLC34A2, SDC4, and CD74, of which CD74 is the most frequently detected in NSCLC.[10] The ROS1 fusion protein is structurally similar to the ALK fusion protein, and so therapeutic strategies for ROS1+ NSCLC and ALK+ NSCLC are similar.

- ROS1 fusions are found almost exclusively in non-squamous tumours, with the majority identified in adenocarcinoma (80–100%).[5, 6, 11] ROS1 fusions are very rare (1–2% of NSCLC)[5, 6, 11-15]and do not commonly overlap with other known oncogenic drivers in NSCLC.[16] Key factors associated with ROS1+ and ALK+ fusion NSCLC are shared; both are primarily found in adenocarcinoma and often occur in younger, non-smoking patients;

- All NSCLC, including those that are ROS1+, is staged as 0, I, II, III or IV according to the tumour, node and metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC).[17] Stage III and IV are considered advanced disease, with Stage III being locally advanced (the cancer has spread to lymph nodes and other organs in the chest) and Stage IV being metastatic disease (the cancer has spread to other parts of the body such as the brain);

- The most common symptoms of advanced lung cancer are fatigue, loss of appetite, weight loss, persistent cough, breathlessness, pain, and ongoing chest infections.[18] Patients may also experience metastasis-related symptoms for example, drowsiness and confusion, severe headaches, sickness and limb weakness in those who develop brain metastases.[18] The symptoms of advanced or metastatic NSCLC can significantly impact patient and carer health-related quality of life (HRQoL);

- The prognosis for patients diagnosed with lung cancer is often poor due to the late diagnosis and only 5% of patients in the UK survive for 10 years or more.[5] ROS1 fusions (along with ALK and neurotrophic tyrosine receptor kinase [NTRK] fusions) have been associated with worse prognosis in cancer.[11] Median progression-free survival (PFS) is approximately 8 months and overall survival (OS) approximately 20 months for patients with ROS1+ NSCLC without ROS1-targeted (based on 103 patients with ROS1+ NSCLC who had mostly received pemetrexed-based chemotherapy);[13]

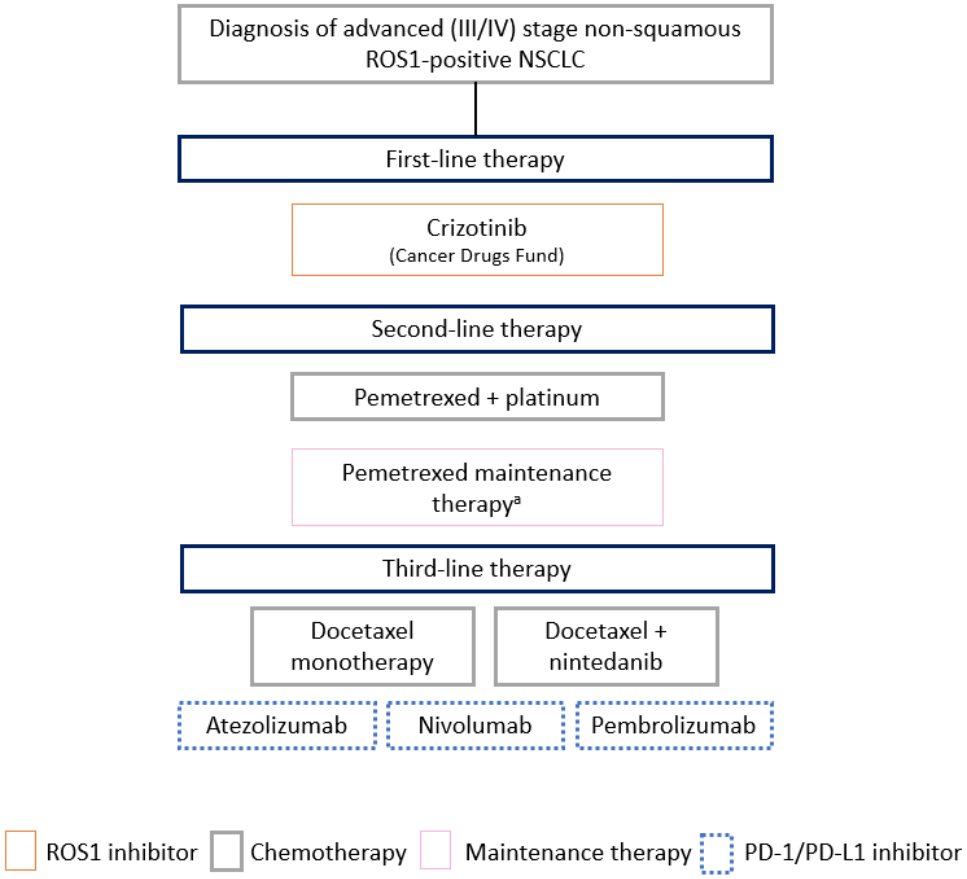
- CNS metastases (including brain metastases) are common in advanced NSCLC and are a major clinical issue. Between 10% to 25% of patients have CNS metastases at the time of diagnosis and up to 50% will develop them at some point during their disease.[19-22] CNS metastases are associated with a significant reduction in quality of life and estimated life expectancy[15, 18] (25.3 weeks compared with 44.9–50.5 weeks for those with contralateral lung, bone, adrenal gland or liver metastases (based on a real-world study).[6]

2.2 Critique of company's overview of current service provision

The company provided a summary of the current clinical pathway of care for ROS1+ NSCLC in the NHS in England (CS Section B.1.3; reproduced as Figure 1). The company's treatment pathway is based on guidance for ROS1+ NSCLC within the NICE pathway for the management of advanced non-

squamous NSCLC (which is based on NG122), but it has been adapted based on clinical consultation and previous NICE committee conclusions (TA529). The ERG provides its critique with reference to the recommendations from NG122 that are relevant to patients with ROS1+ NSCLC, and the related treatment algorithm for systemic anti-cancer therapies (reproduced in Appendix 10.1).

Figure 1. Clinical pathway of care for advanced ROS1-positive NSCLC in NHS England (reproduced from CS Document B, Figure 1)



Abbreviations: NHS, National Health Service; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
Notes: a, only recommended after pemetrexed + cisplatin.
Source: adapted from the NICE pathway for the management of advanced non-squamous (Stages IIIB and IV) NSCLC: ROS1-positive.[23]

The company considers crizotinib the standard first-line treatment for patients with ROS1+ non-squamous NSCLC, which is in line with the NICE pathway for advanced non-squamous NSCLC.[23] The ERG's clinical experts confirmed that crizotinib has displaced chemotherapy as the preferred first-line treatment since it was recommended for use within the Cancer Drugs Fund (CDF) in 2018 (TA529).[12] [14, 24]

Upon progression during first line therapy, the company propose that pemetrexed plus platinum-based chemotherapy (PEM+PLAT), presented as an option in the NICE pathway and treatment algorithm (Appendix 10.1),[25] is the preferred second-line therapy,[23] which was confirmed by the ERG's clinical experts. The NICE pathway also gives platinum doublet chemotherapy – docetaxel, gemcitabine,

paclitaxel or vinorelbine in combination with carboplatin or cisplatin – as a second-line option if the first-line treatment was pemetrexed plus cisplatin, in line with TA181. The company omitted platinum doublets from their pathway because their clinical consultation indicated they are not commonly used to treat patients with non-squamous NSCLC.[12, 14, 25] The ERG's clinical experts advised that, in general, platinum doublets may be used for patients with non-squamous NSCLC if there are no known gene mutations or fusion proteins, but patients who progress on PEM+PLAT are not always candidates for platinum rechallenge and doublets are rarely used to treat ROS1+ NSCLC.[12, 14]

As shown in Figure 1, pemetrexed maintenance treatment is recommended as an option for adults with locally advanced or metastatic non-squamous NSCLC, only if they do not progress immediately after four cycles of PEM+PLAT induction therapy and have ECOG performance status 0 or 1 (TA402).[26] The company's and the ERG's clinical experts estimated that up to 80% of patients will receive pemetrexed maintenance if they are fit enough to receive PEM+PLAT in clinical practice.[14] The ERG heard from clinical experts that platinum maintenance therapy was previously only recommended after pemetrexed plus cisplatin in line with TA402, which is reflected in the NICE final scope. However, the clinical experts reported that the drug acquisition system now allows pemetrexed maintenance therapy to be prescribed after pemetrexed in combination with either cisplatin or carboplatin, and carboplatin is now used for approximately 80% of patients.

The ERG's clinical experts highlighted that quadruple chemotherapy with atezolizumab plus bevacizumab, carboplatin and paclitaxel is now recommended as an option for non-squamous NSCLC, which may include some patients with ROS1+ NSCLC (TA584).[27] The ERG notes that the quadruple therapy is only recommended first line for patients with PD-L1 expression between up to 49%, or after failure of targeted therapy for EGFR+ or ALK+ NSCLC (TA584).[28] The ERGs clinical experts consider the atezolizumab quadruple therapy as a possible second-line treatment option after crizotinib for patients with ROS1+ NSCLC, although it is unclear whether patients will be subject to the same condition as those with EGFR+ or ALK+ NSCLC regarding prior targeted therapy.

On progression after second-line therapy, NICE-recommended treatments include docetaxel with or without nintedanib (for those with adenocarcinoma histology, TA347[29]), and the immunotherapies nivolumab (TA484), atezolizumab (TA520) and pembrolizumab (TA428).[23, 30-32] The ERG's clinical experts reported that docetaxel is rarely used and immunotherapies would be preferred at third-line if patients remain well enough to tolerate treatment. The experts highlighted that, after TKI options are exhausted, treatment choice will vary because the efficacy of current treatments is poor, and so clinical trials for other new drugs may be considered if the patient meets the trial eligibility criteria.

The anticipated marketing authorisation for entrectinib is [redacted]

[redacted] in ROS1+ NSCLC following confirmation of ROS1+ status. The ERG's clinical experts confirmed that patients with non-squamous NSCLC tumours are now routinely tested for known mutations and protein fusions at diagnosis, in line with the 2019/2020 National Genomic Test Directory for Cancer[7], so no additional costs are anticipated for testing. Entrectinib is an oral treatment so will not require additional administration costs, and no specific side-effects have emerged that would require a change to current management. The company state that treatment with entrectinib is recommended until disease progression or unacceptable toxicity (CS, Table 2). The company's and ERG's clinical experts anticipate that entrectinib would likely displace crizotinib as the first choice for untreated, advanced or metastatic ROS1+ NSCLC. The experts suggested that entrectinib may be used after crizotinib in some circumstances, at which point the relevant comparator is likely to be PEM+PLAT. The ERG discusses the company's choice of comparator treatments in their evidence submission in Section 3.3.

The ERG's clinical experts explained that patients commonly develop resistance to crizotinib at some point during treatment which usually means there will be limited to no benefit from subsequent TKIs. The experts explained that, if entrectinib is given first line as proposed by the company, there would be no benefit expected from crizotinib and PEM+PLAT would be the most appropriate second-line therapy. The ERG's clinical experts outlined that PEM+PLAT is the most common choice for patients with ROS1+ NSCLC if there are no TKI options available, but an immunotherapy may be given (e.g. nivolumab or pembrolizumab), or potentially the quadruple atezolizumab combination since its recent recommendation (after the scope was finalised). However, entrectinib might be considered after first-line crizotinib because it may offer additional benefits for CNS disease, and treatment choices thereafter would be the same as if entrectinib had been given first line. As stated above, treatment choice varies after targeted therapy options have been exhausted, and patients can be reluctant to switch from oral TKI therapy to intravenous chemotherapies. Generally, a new treatment will be initiated after progression if the patient is well enough to tolerate it, in which case best supportive care will be provided.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided an outline of the decision problem addressed in the company's submission (CS) in relation to the final scope issued by the National institute for Health and Care Excellence (NICE; Table 1), including a rationale for any deviations. The evidence review group's (ERG's) critique is provided in the sections that follow.

Table 1. Summary of decision problem as outlined in the company's submission (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer	People with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer	N/A
Intervention	Entrectinib	Entrectinib	N/A
Comparator(s)	**Untreated disease:** •Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment •Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment •Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy **After previous chemotherapy treatments:** •Docetaxel, with (for adenocarcinoma histology) or without nintedanib	•Crizotinib •Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment	Entrectinib is intended for use in the first- or second-line setting and is directly targeting CDF reimbursement. Crizotinib is the most clinically relevant comparator in this setting, and as a CDF funded treatment, is arguably the most relevant comparator from a funding perspective. Crizotinib is therefore included alongside pemetrexed plus platinum as relevant comparators to the decision problem. The company's rationale for each comparator not considered is detailed in Section 3.3.
Outcomes	The outcome measures to be considered include: •OS •PFS •Response rate •Time to treatment discontinuation •AEs of treatment •Health-related quality of life	As per final scope	N/A
Subgroups to be considered	If the evidence allows, consideration will be given to subgroup based on the presence or absence of brain metastases.	Consideration of the clinical effectiveness is given to subgroup based on the presence or absence of brain metastases.	The limited overall size of the trial population and the smaller CNS population prohibits separate comparative effectiveness and cost-effectiveness analysis of this subgroup.

Abbreviations: CDF, Cancer Drugs Fund; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ERG, evidence review group; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

3.1 Population

The final scope issued by NICE outlines the population for this technology appraisal to be people with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer, which is hereafter referred to as ROS1+ NSCLC. The ERG highlights that the NICE final scope does not specify age but the evidence for entrectinib in ROS1+ NSCLC is currently limited to adults ≥ 18 years. An ongoing paediatric study of entrectinib is mentioned in the CS (STARTRK-NG) and has not yet recruited any children with ROS1+ NSCLC (CS, page 19), and so the discussion henceforth is relevant only to adults with ROS1+ NSCLC.

The clinical effectiveness evidence for entrectinib submitted by the company is based on an integrated analysis across the clinical trial programme, which comprises of three ongoing single-arm trials: two Phase I studies (ALKA,[33] STARTRK-1[34]) and one Phase II study (STARTRK-2[35]). The studies recruited patients with a variety of advanced or metastatic solid tumours testing positive for ROS1, ALK, or NTRK1/2/3 genetic alterations (CS, Table 4). The integrated analysis underpinning the CS was based on a ROS1+ NSCLC primary efficacy set of patients across the three studies who had:

- A confirmed diagnosis of ROS1+ NSCLC;
- measurable disease at baseline;
- at least 12 months' follow-up from the time of first response;
- no prior ROS1 inhibitor treatment.

At the clarification stage, the ERG asked for details of how the efficacy set was defined, which reduced the total number of enrolled patients with ROS1+ NSCLC from [redacted] (safety population) to 53 (CS, Figure 2). Patients were most commonly excluded for having less than 12 months' follow-up from first response ([redacted]) and the remaining [redacted] had received a prior ROS1 inhibitor (n = 27) or were subsequently found to be ineligible due to ECOG performance status (n = 3), lack of measurable disease at baseline (n = 3), or ROS1 biomarker (n = 1). The ERG understood that [redacted] patients in the company's primary efficacy set received doses higher ([redacted]) or lower ([redacted]) than the recommended starting dose.

The ERG's clinical experts agreed that it was appropriate to include only patients with ROS1+ NSCLC and considered it reasonable to exclude patients without measurable disease at baseline to allow for response and progression outcomes to be captured. The experts also agreed that it is appropriate to focus on patients who were naïve to ROS1-inihibitors, given that entrectinib will most likely be the first choice of targeted treatment. However, the ERG was keen to remove the minimum follow-up restriction because it was concerned that it introduced selection bias, and because patients with no events during

shorter follow-ups contribute useful information for key survival outcomes (OS and PFS) through censoring. At the clarification stage, the company explained that the minimum follow-up was used at the request of the United States Food and Drug Administration (FDA) to assess durability of response, [redacted].

The ERG was also concerned that some patients in the analysis received entrectinib at doses outside the proposed marketing authorisation. The ERG notes that the recommended starting dose of entrectinib is 600 mg which can be reduced in the event of toxicities or pre-existing conditions (draft summary of product characteristics [SmPC]). Only a small number of patients in the company's primary efficacy set started at doses above or below 600 mg, but the number once the follow-up restriction was removed was unknown, and so the ERG asked for the population to be limited to patients who received the recommended starting dose. The company confirmed that all patients in STARTRK-2 received 600 mg but could not be definitive about which patients received the recommended starting dose of 600 mg in STARTRK-1 and ALKA. Therefore, the ERG considers an analysis based only on STARTRK-2 more appropriate for decision making in line with the proposed marketing authorisation. The ERG's preferred efficacy population includes patients from STARTRK-2 with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline, regardless of follow-up duration (n = 78).

[redacted], patients' with ROS1+ NSCLC in each of the entrectinib studies underpinning the submission had ROS1 status established with a validated assay prior to treatment initiation. The company explain that the molecular characterisation of tumour tissue was evaluated in several ways in the individual studies. However, only with ROS1 gene fusions detected by a nucleic acid-based method and predicted to translate into a fusion protein with a functional kinase domain were included in the ROS1+ integrated analysis. The ERG's clinical experts outlined that patients with non-squamous NSCLC tumours (and selective patients with squamous NSCLC who are young and/or have minimal smoking history), are now tested routinely in the NHS for known genetic alterations for which targeted therapy is available. The ERG notes that ROS1 testing is now included in the 2019/2020 National Genomic Test Directory for Cancer after crizotinib was made available through the CDF in 2018.[7, 12]

The ERG's clinical experts considered the baseline characteristics of the company's original integrated analysis (reproduced in Appendix 10.2) and those for each study individually reflective of what is known about patients affected by ROS1+ NSCLC in England (often young and non-smokers with a higher prevalence of CNS metastases; see Section 2). Baseline characteristics were also provided for the ERG's preferred efficacy set, which are compared with those of the company's preferred population in Section 4.2.3. The company submitted subgroup results for patients with CNS metastases at baseline in line with the scope, which was highlighted by the ERG's clinical experts as a key effect modifier for prognosis and quality of life (CS, Table 5).

The NICE final scope did not restrict the population by prior treatment but listed comparators separately for untreated disease and after chemotherapy. Approximately two thirds of the company's primary efficacy set (67.9%) and slightly more of the ERG's preferred efficacy set (73.1%) had received one or more systemic treatment before entrectinib (see Appendix 10.2), meaning there were very few patients on which to base an assessment of entrectinib in a purely untreated population. Advice from the ERG's clinical experts suggests that the impact of prior treatments on the assessment of entrectinib at first line is mitigated by the exclusion of patients who had received prior ROS1 inhibitors, which would have the biggest impact on the benefits of entrectinib. The experts do not expect prior chemotherapy treatments to have a major impact on the absolute estimates of effectiveness, but there may be an impact of other prior targeted therapies and immunotherapies (covered in Section 4.2.3).

The company intend for entrectinib to be used primarily for untreated disease, but the ERG's clinical experts explained that it would have been impractical to run a first line trial for rare cancer subtypes. As a result, the treatment effects based on the largely pre-treated population who received entrectinib may underestimate the potential benefit of entrectinib for patients with untreated ROS1+ NSCLC. However, comparative estimates of entrectinib versus crizotinib for untreated disease are based on a matching adjusted indirect comparison (MAIC) with a study population that had also received a range of prior therapies, so relative effects should not bias against entrectinib. The study used to conduct an MAIC of entrectinib with PEM+PLAT was in an untreated proxy population with ALK+ NSCLC but was not the company's chosen method of generating estimates for that comparison in the economic model (described further in Section 4.4).

3.2 Intervention

The NICE final scope lists entrectinib as the intervention of interest, which matches the intervention delivered in each of the single-arm studies contributing to the integrated analysis underpinning the company's submission (ALKA, STARTRK-1, STARTRK-2). The company provides an overview of the technology being appraised in Table 2 of their submission, which states that entrectinib (RO7102122; formerly known as RXDX-101 and NMS-1191372) is an oral, CNS-active, potent inhibitor of the tyrosine kinases encoded by the ROS1, NTRK1, NTRK2, NTRK3 and ALK genes. Marketing authorisation from the European Medicines Agency (EMA) for entrectinib [redacted] is anticipated in [redacted] ((information provided by the company during the factual accuracy check)). The company highlights that marketing authorisation is also being sought for NTRK+ solid tumours which is of relevance to NICE technology appraisal GID-TA10414 (CS, Table 2).

The CS [redacted] state the dose of entrectinib as 600 mg, to be taken as three 200 mg oral capsules once daily, which can be reduced in the event of toxicities or pre-

existing conditions. Clinical study reports (CSRs) provided by the company show that doses ranged from [redacted] in ALKA (ALKA CSR, Figure 2)[33] and from [redacted] in STARTRK-1 (STARTRK-1 CSR, Figure 2),[34] which led to the selection of 600 mg for STARTRK-2. In addition, a protocol amendment in STARTRK-2 [redacted]. The ERG asked the company to clarify starting doses given to patients in their primary efficacy set (n =53) and the population across studies without excluding patients with less than 12 months follow-up. The company could not confirm starting doses in the Phase I studies, and so the ERG's efficacy set was limited to patients in STARTRK-2 who all received a starting dose of 600 mg .

The company indicates that treatment with entrectinib is recommended until disease progression or unacceptable toxicity (CS, Table 2 [redacted], Appendix C), and the CSRs confirm that entrectinib was delivered as such in ALKA, STARTRK-1 and STARTRK-2. Other reasons for discontinuation of study treatment in the studies were patient refusal and withdrawal of consent, otherwise there was no limit on the number of cycles a patient could receive. The ERG's clinical experts explained that rules for treatment discontinuation are in line with how entrectinib would be managed in clinical practice, except that the measurement of disease progression is more closely managed in clinical trials and measured objectively according to RECIST. In clinical practice, treatment may continue beyond the first signs of progression if the treating clinician judges that there is an ongoing benefit of treatment.

3.3 Comparators

The comparators in the NICE final scope are listed separately for untreated disease and after previous chemotherapy treatments, whereas the company take what is termed an 'all lines approach' in their submission. The ERG's clinical experts agree that, should entrectinib be recommended for ROS1+ NSCLC, it will most likely be used as first-line treatment and possibly as second-line treatment after crizotinib. As addressed in Section 3.1, 67.9% of patients in the company's preferred efficacy population and 73.1% of the ERG's preferred population had received one or more systemic therapy (see Appendix 10.2) and the ERG agrees with the company that the number of patients studied makes it impractical to assess entrectinib separately for untreated and previously treated ROS1+ NSCLC. The ERG's clinical experts highlighted the difficulty in running trials for rare and advanced cancers and so the ERG critiques the choice of comparators in light of the paucity of evidence in ROS1+ NSCLC.

3.3.1 Comparators covered in the company's submission

Comparators presented in the CS are not in line with the final scope, but the ERG's clinical experts agreed that the comparisons made in the submission cover treatments that are most commonly used for

the first- and second-line treatment of ROS1+ NSCLC in UK clinical practice (see Section 2.2). The ERG provides its critique with reference to sections of NG122 and the treatment algorithm for systemic anti-cancer therapies that are relevant to patients with ROS1+ NSCLC (see Appendix 10.1).

Crizotinib for untreated disease

Crizotinib was not listed in the NICE final scope because it is only available through the CDF (TA529),[36] but the ERG's clinical experts agree with the company that it is now the preferred treatment for untreated ROS1+ NSCLC. It is the only TKI recommended for patients with ROS1+ NSCLC (TA529) and, as the most effective treatment, would always be used first. The clinical experts advised that it has displaced PEM+PLAT as the preferred first-line treatment for ROS1+ NSCLC and is the most relevant comparator for entrectinib. The ERG's clinical experts expressed that the inclusion of ROS1 testing in the national test directory will mean patients who might otherwise have received PEM+PLAT are now more likely to be picked up at diagnosis and receive crizotinib first-line.

The company acknowledge NICE's position regarding comparators within technology appraisals that are available via the CDF but consider crizotinib an appropriate comparator given that the company are actively seeking a CDF recommendation for entrectinib (CS, pg. 7). The company also outline that [redacted].

The only available evidence for entrectinib for patients with ROS1+ NSCLC is from non-comparative single-arm studies, and so an unanchored MAIC with a single-arm study of crizotinib in a similar ROS1+ NSCLC population was conducted (PROFILE 1001).[37] A critique of the company's choice of study and the methods used to provide comparative estimates are provided in Section 4.4.

Pemetrexed plus platinum therapy (with or without pemetrexed maintenance therapy)

The ERG's clinical experts agreed with the company that PEM+PLAT is a relevant comparator because it would be the preferred option when a patient progresses on crizotinib. The experts explained that patients commonly develop resistance to crizotinib at some point during treatment and the benefit of a subsequent TKI will be dependent on the type of resistance and site of progression. The range of resistant mechanisms continues to be a subject of investigation but, in the context of intracranial progression, entrectinib provides an alternative to PEM+PLAT after progression on crizotinib because its activity in the CNS is higher than either PEM-PLAT or crizotinib.

The ERG's clinical experts highlighted that pemetrexed maintenance therapy was previously only recommended for use after pemetrexed plus cisplatin (in line with TA402, as stated in the NICE final scope) but can now also be given after pemetrexed plus carboplatin (see Section 2.2). Therefore, on

advice from clinical experts, the ERG expects that most patients who receive PEM+PLAT also receive pemetrexed maintenance therapy, and carboplatin is now more often the chosen platinum agent.

3.3.2 Comparators not considered relevant

After consulting clinical experts, the ERG agrees that the remaining comparators listed in the NICE final scope are not relevant because they are all used later in the pathway after crizotinib and PEM+PLAT, whereas entrectinib will be used as an alternative to first- and second-line treatments. The company's rationale and comments from the ERG's clinical experts for each comparator not considered are provided in Appendix 10.3.

3.4 Outcomes

The company presented data for all outcomes listed in the NICE final scope for the company's primary efficacy set (CS Section B.2.6) and for the ERG's preferred efficacy set outlined at the clarification stage (Section 3.1), namely:

- Overall survival;
- Progression-free survival
    - Assessed by investigators and by blinded independent central review (BICR) according to Response Evaluation Criteria for Solid Tumours (RECIST);
    - Time to CNS progression by BICR was also presented to demonstrate the protective benefit of entrectinib for CNS progression;
- Response rate
    - Complete response (CR), partial response (PR), overall response rate (ORR, defined CR or PR), stable disease (SD), clinical benefit rate (CBR, defined as CR, PR or SD for ≥ 6 months), best overall response (BOR) and duration of response (DOR) by BICR;
- Time to treatment discontinuation;
- Adverse effects (AEs) of treatment (for the ROS1 safety population [redacted], and the total safety population including other indications [redacted])
    - AEs of any grade (overall and judged to be related to treatment), AEs of Grade 3 and above (overall and related to treatment), AEs requiring dose reduction, interruption or discontinuation, common AEs (≥ 10% of patients) and serious adverse events (SAEs);

- Health-related quality of life
    - Including the EuroQoL 5-Dimensions (EQ-5D), the European Organization for Research and Treatment Quality of Life Core Questionnaire (EORTC-QLQ-C30)[38] and lung cancer module (QLQ-LC13).[39]

The ERG notes that data for key survival outcomes (OS and PFS) are immature at both clinical cut-off dates (CCOD: 31 May 2018 and 30 October 2018) submitted by the company, meaning the most mature data for the benefit of entrectinib is for tumour response. The ERG notes that there is some correlation between ORR and PFS within trials of targeted treatments for NSCLC, but no association has been found between ORR and OS, which is considered in the critique of clinical effectiveness results.[40]

Time to treatment discontinuation (TTD) data were collected in ALKA, STARTRK-1 and STARTRK-2 but results were not described with the company's clinical effectiveness results. The company use the study TTD data to model time on treatment for the economic model, so results are critiqued with the cost-effectiveness results.

Outcomes chosen for the MAIC with crizotinib and PEM+PLAT were OS, PFS, ORR, any SAE, any Grade 3+ AE and treatment discontinuation due to AE (CS Section B.2.9). The company did not give a reason for not considering HRQoL for the MAIC. The statistical approach to the entrectinib integrated analysis and the unanchored MAIC required to provide comparative estimates are critiqued in Section 4.2.4 and Section 4.4.2, respectively.

PFS, OS and response outcomes were presented separately for the subgroup of patients with CNS metastases at baseline (CS, Section B.2.7), although results were limited by patient numbers and the subgroups are not reflected in the economic model. Results for a range of other subgroups were provided for ORR, the primary outcome in the single-arm entrectinib studies, using the primary integrated efficacy set (n = 53; CS, Appendix E), which are covered in Section 4.3.7.

3.5 Other relevant factors

The company refer to the equality consideration relating to access to ROS1-targeted therapy due to regional variation in testing that was raised during TA529[12] (CS, pg. 18). The ERG agrees with the company that ROS1 testing is now part of the standard diagnostic workup and is included in the 2019/2020 National Genomic Test Directory for Cancer, so there is no longer an equality issue. [redacted]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company carried out systematic literature reviews (SLRs) to identify relevant clinical effectiveness evidence to inform the indirect comparisons of entrectinib versus crizotinib and pemetrexed plus platinum therapy (PEM+PLAT). Evidence was first sought for patients with locally advanced or metastatic ROS1-fusion positive non-small-cell lung cancer (hereafter referred to as ROS1+ NSCLC) and, where none was identified, evidence was sought for a proxy population with locally advanced or metastatic anaplastic lymphoma kinase positive (ALK+) NSCLC.

The company's SLRs are summarised in Table 2 with a comment from the evidence review group (ERG) about the appropriateness of the methods adopted. Further critique is provided in Appendix 10.5.

Table 2. Summary of the ERG's critique of the company's ROS1+ and ALK+ NSCLC SLRs

Review step	CS Section	ERG critique
Data sources	CS Appendix D.1, page 4–5	**The ERG considers the sources and dates searched comprehensive** Embase, MEDLINE and MEDLINE In-Process, Cochrane Library (CENTRAL, DARE, CDSR, HTAD), conference proceedings (last three years of ASCO, ESMO, WLCC, ELCC, BTOG), trial registries (ct.gov, EUCTR and WHO ICTRP), HTA websites for UK, France and Germany, SR reference lists. ERG notes that the DARE and HTAD strategies not provided and are no longer included in the Cochrane Library.
Search strategies	CS Appendix D.1, Tables 1–9, page 6–34	**The ERG is satisfied that searches would have identified all evidence relevant to the decision problem** Searches combined comprehensive condition terms with terms for fusion proteins (ROS1 or ALK; not for entrectinib or crizotinib), comparators and study design. October 2018 updates were expanded to all dates, and the ROS1 SLR was expanded to include observational study terms.
Inclusion criteria	CS Appendix D.1, Table 10, page 34–37	**The ERG has reservations about using the proxy ALK+ population to provide a comparison with PEM+PLAT, but otherwise considers the eligibility criteria appropriate** Reproduced in Appendix 10.5. Criteria were at least as broad as the NICE final scope but the decision process for carrying studies forward for the MAIC was not prespecified or well described. Observational studies were excluded from the ALK+ SLR but it is a proxy population for which RCT evidence is preferable.
Screening and data extraction	Appendix D.1, page 34 and 37	**The ERG has some concerns about the transparency of study inclusion and the rationale of choosing studies for the MAIC** Otherwise the methods described were robust (independent duplicate screening by two reviewers with predefined criteria; discrepancies resolved by consensus/with a third reviewer; data extracted by a single reviewer and verified by a second).
Quality assessment	CS Section B.2.5, Appendix D.3	**ERG considers the company's quality assessments satisfactory** Entrectinib integrated analysis and PROFILE 1001 (crizotinib MAIC) assessed with Downs and Black checklist. ASCEND-4 (PEM+PLAT MAIC) assessed according to NICE user guide for critical appraisal of RCTs. No other studies quality-assessed.

Abbreviations: ALK+, anaplastic lymphoma kinase positive; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company's submission; ct.gov, clinicaltrials.gov; DARE, Database of Abstracts of Reviews of Effects; ERG, Evidence Review Group; EUCTR, European Union Clinical Trials Register; MAIC, matching adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; NSCLC, non-small-cell lung cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; RCT, randomised controlled trial; SLR, systematic literature review; SMC, Scottish Medicine Consortium; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

The entrectinib studies ALKA, STARTRK-1 and STARTRK-2 did not appear in the SLRs because they have not yet been published, but three further studies were chosen from the results to support matching indirect treatment comparisons (MAIC) between entrectinib and the comparators of interest (see Section 4.4.1 for details):

- PROFILE 1001, a Phase I single-arm study of crizotinib in an ROS1+ NSCLC, was chosen to support an MAIC of entrectinib and crizotinib:

- ASCEND-4, a Phase III RCT of ceritinib versus pemetrexed plus platinum chemotherapy (PEM+PLAT) in the proxy ALK+ NSCLC population, was chosen in the absence of evidence in a ROS1+ NSCLC population to inform an MAIC of entrectinib versus PEM+PLAT;

- PROFILE 1007, a Phase III RCT of crizotinib versus pemetrexed or docetaxel monotherapy in the proxy ALK+ NSCLC population, was chosen in the absence of evidence in a ROS1+ NSCLC population to support a secondary MAIC of entrectinib versus docetaxel.

The ERG has reservations about the search and inclusion of evidence for ALK+ NSCLC where none was identified for PEM+PLAT in a ROS1+ NSCLC population, which are described further with results of the MAICs (Section 4.4).

Neither the ERG nor the company consider docetaxel a relevant comparator for entrectinib and so the ERG focuses its critique on the studies chosen for crizotinib and PEM+PLAT (see Sections 2.2 and 3.3). The company do not use the ASCEND-4 MAIC to estimate relative treatment effects in the economic model, and instead apply hazard ratios for crizotinib versus PEM+PLAT from PROFILE 1014 to the results from the entrectinib versus crizotinib MAIC (discussed in 4.4).

The Phase II OxOnc and AcSe studies in ROS1+ populations[41, 42] also provide evidence for crizotinib in ROS1+ NSCLC populations, but the ERG's clinical experts considered PROFILE 1001 the most robust evidence source for the indirect treatment comparison. The ALK+ study, ASCEND-4, was chosen for the PEM+PLAT MAIC in the absence of PEM+PLAT data for patients with ROS1+ NSCLC, but the pros and cons of other RCTs in ALK+ populations are not considered in detail (e.g. PROFILE 1014, ASCEND-5, PROFILE 1029; see Table 58). ASCEND-4 was deemed the most appropriate because it is the only study to have given pemetrexed maintenance therapy, which most patients receive after PEM+PLAT induction therapy UK clinical practice but other factors such as length of follow-up, sample size, study quality, and robustness of outcome data were not considered in the feasibility assessment.

The company presented a quality assessment of the entrectinib integrated analysis of ROS1+ NSCLC patients from ALKA, STARTRK-1 and STARTRK-2 which was undertaken using the Downs and

Black checklist[43] (CS pg. 37 and CS Appendix D.3, Table 28). Quality assessments were also conducted for the studies chosen for the MAICs using appropriate tools for the study design (Downs and Black for PROFILE 1001 and according to the NICE guide for critical appraisal of RCTs for ASCEND-4 and PROFILE 1007). Quality assessments were not conducted for any other studies identified in the SLRs that were considered for the MAICs. Overall, the ERG is satisfied that all relevant evidence was identified in the company's SLRs and that PROFILE 1001 is the most appropriate study to compare entrectinib with crizotinib for ROS1+ NSCLC. The use of ASCEND-4 for the entrectinib versus PEM+PLAT comparison was not justified fully, and the ERG was unable to investigate all alternatives within the time available, but alternative studies are all subject to the same uncertainties of using an ALK+ population as a proxy for ROS1+ NSCLC.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Clinical effectiveness evidence submitted by the company is based on an integrated analysis of three ongoing Phase I (ALKA, STARTRK-1) and Phase II (STARTRK-2) single-arm studies that support the application for marketing authorisation for entrectinib for ROS1+ NSCLC. Section 3 outlines the ERG's critique of the evidence submitted from ALKA, STARTRK-1 and STARTRK-2 in relation to the decision problem outlined in the NICE final scope. The studies recruited patients with a variety of advanced or metastatic solid tumours testing positive for ROS1, ALK, or NTRK1/2/3 genetic alterations (CS, Table 4). A fourth study, STARTRK-NG, which recruited a paediatric population with a variety of tumour types was not included because no patients with ROS1+ NSCLC have been recruited.

The primary efficacy set for the company's integrated analysis includes 53 patients from ALKA, STARTRK-1 and STARTRK-2 with ROS1-inhibitor naïve ROS1+ NSCLC, measurable disease at baseline, and at least 12 months' follow-up from first response (see Section 4.2.4 for a diagram showing patient eligibility for the company's analysis populations). The ERG agreed with the rationale to pool patients with ROS1+ NSCLC from the Phase I and II studies to increase the number of patients included but preferred no follow-up restriction ([redacted] patients had been excluded for this reason) and for any patients who received entrectinib at doses outside the proposed marketing authorisation (600 mg once daily as three 200 mg oral capsules) to be excluded from the analysis. The ERG wanted to remove the minimum follow-up restriction because it was concerned that it introduced selection bias, and because patients with no events during shorter follow-ups contribute useful information for key survival outcomes (OS and PFS) up to the point at which they would be censored. The company was able to remove the follow-up restriction but was unable to restrict the integrated efficacy set by dose because it could not confirm what doses of entrectinib patients received in the Phase I studies (ALKA and STARTRK-1). Consequently, the ERG's preferred efficacy set includes only patients from STARTRK-2 (n = 78) because it gave entrectinib within its proposed marketing authorisation.

Key study characteristics of ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG are shown in Table 3, which are described and critiqued in the sections that follow. Full eligibility criteria, detailed data collection and drug administration procedures and allowed and disallowed concomitant medications for each study were provided in Appendix L.1 of the company's submission and have not been reproduced by the ERG. Where necessary, patient baseline characteristics, methods of analysis and clinical effectiveness results are described separately for the company's and the ERG's preferred efficacy sets.

The studies included a mix of treatment-naïve and previously treated patients (who had received a range of treatments) and, given the limited number of patients available, the company use the whole cohort for its indirect analyses with comparator treatments. The ERG is mindful that the type and number of prior treatments may impact the absolute treatment effects of entrectinib and, more importantly, relative treatment effects from the matching adjusted indirect comparison (MAIC) where differences in prior treatments between the entrectinib population and other studies could not be adjusted for. The ERG agrees with the company that the number of patients with ROS1+ NSCLC makes formal subgroup analysis by line of treatment impractical and so highlights the likely presence and direction of bias in its critique of the MAIC (Section 4.4).

Table 3. Clinical effectiveness evidence for entrectinib (merged from CS Tables 3 and 4)

Study	ALKA (ALKA-372-001)	STARTRK-1 (RXDX-101-01)	STARTRK-2 (RXDX-101-02)	STARTRK-NG (RXDX-101-03)
Study design	•Ongoing •Phase I, first-in-human •Single-arm, open-label •Multicentre •Dose escalation in 3+3 scheme	•Ongoing •Phase I •Single-arm, open-label •Multicentre •Dose escalation in 3+3 scheme plus dose expansion	•Ongoing •Phase II •Single-arm, open-label •Multicentre •Registration-enabling basket study	•Ongoing •Phase I/II •Open-label •Dose escalation and expansion
Location	2 centres in Italy	11 centres in the US, South Korea and Spain	84 centres in 15 counties across 4 continents (Australia, Europe, Asia and the US)	Not described
Population/eligibility	•Adults (≥18 years) with advanced or metastatic solid tumours with TRKA/B/C, ROS1, or ALK molecular alterations o Including those with controlled asymptomatic CNS disease •No effective standard therapy available, suitable or accepted as an alternative to trial enrolment •No previous targeted treatment for genetic alterations but other prior cancer therapy allowed •ECOG performance status ≤2 •No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis •Not enrolled in another therapeutic study	•Adults (≥18 years) with advanced or metastatic solid tumours with NTRK, ROS1, ALK or other molecular alterations (for dose expansion) o Including those with controlled asymptomatic CNS disease •No effective standard therapy available, suitable or accepted as an alternative to trial enrolment •Previous TKI for NTRK+ disease •Prior cancer therapy allowed including targeted treatment (except prior entrectinib) •ECOG performance status ≤2 •No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis, peripheral neuropathy Grade ≥2 or history of TKI-induced pneumonitis •Not enrolled in another therapeutic study	•Adult patients with advanced/ metastatic solid tumours with NTRK, ROS1, or ALK genetic alterations o Including those with controlled asymptomatic CNS disease •No previous targeted treatment for genetic alterations but other prior cancer therapy allowed •ECOG performance status ≤2 •No active infection, GI disease, known interstitial lung disease, or interstitial fibrosis •No peripheral neuropathy Grade ≥2 or history of TKI-induced pneumonitis •Not enrolled in another therapeutic study	•Age 2 to 21 years •Relapsed or refractory extracranial solid tumours (Phase I) •Expansion cohorts in patients with primary TRK, ROS1, or ALK brain tumours, neuroblastoma, and other TRK, ROS1, or ALK extracranial solid tumours (Phase Ib)
Intervention	Entrectinib 100mg/m^2 to 1600mg/m^2 given orally according to varying schedules	**Dose escalation segment:** Entrectinib 100mg/m^2 given orally once daily and escalated in a conventional "3+3" scheme up to MTD	Entrectinib 600mg given orally (as three 200mg capsules) once daily (with option to escalate to 800 mg for patients with brain metastases)	Not described

		Dose expansion segment: Entrectinib 600mg given orally (as three 200mg capsules) once daily		
Comparator	N/A	N/A	N/A	N/A
Total recruited	58	76	207	16
Supports application for marketing authorisation	Yes	Yes	Yes	No
Used for economic model	Yes	Yes	Yes	No
Rationale for use/non-use in the model	Clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	Clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	Clinical evidence in support of entrectinib in the population directly relevant to the decision problem.	Clinical evidence in support of entrectinib not directly relevant to decision problem.
Reported outcomes specified in the decision problem	•Objective Response Rate •Duration of Response •Progression-free Survival •Overall Survival •TTD •Adverse effects of treatment	•Objective Response Rate •Duration of Response •Progression-free Survival •Overall Survival •TTD •Adverse effects of treatment	•Objective Response Rate •Duration of Response •Progression-free Survival •Overall Survival •TTD •Adverse effects of treatment •Health-related quality of life	•Objective Response Rate •Progression-free Survival •Overall Survival •Adverse effects of treatment
All other reported outcomes	•Disease Control •Dose-Limiting Toxicity •Maximum Tolerated Dose •Recommended Phase 2 Dose •Plasma Concentrations of Entrectinib	•Disease Control •Dose-Limiting Toxicity •Maximum Tolerated Dose •Recommended Phase 2 Dose •Plasma Concentrations of Entrectinib	•Time to Response •Clinical Benefit Rate •Intracranial Tumour Response •CNS Progression-free Survival	•Dose-Limiting Toxicity •Maximum Tolerated Dose •Recommended Phase 2 Dose •Plasma Concentrations of Entrectinib
Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; MTD, maximum tolerated dose; N/A, not applicable; NSCLC, non-small cell lung cancer; TTD, time to treatment discontinuation.				

4.2.1 Trial conduct

4.2.1.1 ALKA (ALKA-372-001)

ALKA is an ongoing single-arm, open-label Phase I study which is the first to investigate oral entrectinib as a single agent in humans (CS, pg. 22), and had the primary aim of identifying first-cycle dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) of entrectinib. ALKA is being conducted exclusively in Italy and has recruited 58 adult patients with locally advanced or metastatic NTRK+, ROS1+ or ALK+ solid tumours (including those with controlled asymptomatic CNS metastases). Patients were not eligible if they had an active infection, gastrointestinal (GI) disease, interstitial lung disease or fibrosis, ECOG performance status greater than 2 (indicating limited mobility and self-care), or had received prior targeted therapy for genetic alterations, but other prior cancer therapies were allowed (Table 3). Patients were only eligible if no effective standard therapy was available, suitable or accepted as an alternative to trial enrolment

Patients were enrolled during dose escalation into cohorts using a "3+3" scheme and received doses of entrectinib ranging from 100 mg/m^2 to 1600 mg/m^2 given orally in varying schedules (continuous dosing or with off-treatment breaks). Objective response rate (ORR) was specified as an endpoint in the protocol and the CS states that exploratory evaluations of duration of response (DoR), progression-free survival (PFS) and overall survival (OS) were planned for the overall treated population (CS, Table 4). The ERG understands that evaluation of the additional efficacy endpoints for patients with ROS1+ NSCLC in an integrated analysis with STARTRK-1 and STARTRK-2 were not prespecified. However, the company state that the ROS1+ NSCLC integrated analysis was accepted by the European Medicines Agency (EMA) and United Stated Food and Drug Administration (FDA) in light of the rare disease setting (CS, pg. 19).

The ERG considers ALKA unreliable to provide evidence in support of the clinical effectiveness of entrectinib for the population of interest to this STA, given its aim as a Phase I study, the range of doses assessed, and the small number of patients with ROS1+ NSCLC recruited.

4.2.1.2 STARTRK-1 (RXDX-101-01)

Like ALKA, STARTRK-1 is an ongoing single-arm, open-label Phase I study with the primary aim of identifying first-cycle DLT and the MTD of entrectinib in patients with a range of locally advanced or metastatic NTRK+, ROS1+ or ALK+ solid tumours (including those with controlled asymptomatic CNS metastases). STARTRK-1 is being conducted in the USA, South Korea and Spain and has recruited 76 patients. Like the ALKA study, patients were not eligible if they had an active infection, gastrointestinal (GI) disease, interstitial lung disease or fibrosis, ECOG performance status greater than 2 (indicating limited mobility and self-care). Patients were only eligible if no effective standard therapy

was available, suitable or accepted as an alternative to trial enrolment. However, unlike the ALKA study, patients were eligible if they had received any prior cancer therapy, including targeted therapies (Table 3).

STARTRK-1 consisted of dose escalation and dose expansion segments. In the dose escalation segment, patients were enrolled into cohorts using a "3+3" scheme, starting at 100 mg/m^2 of entrectinib up to the MTD (Table 3). In the dose expansion segment, patients received 600 mg daily as three 200 mg capsules (RP2D), the dose selected for further investigation in the Phase II STARTRK-2 study. ORR was the primary efficacy outcome during dose escalation but, unlike ALKA, further efficacy endpoints were prespecified for both the dose escalation and dose expansion segments (clinical benefit rate [CBR], DoR, PFS, and OS). Intracranial tumour response in patients with CNS disease was also explored in the dose expansion segment. (CS, Table 4).

The ERG considers STARTRK-1 more robust than ALKA due to the dose expansion segment, during which patients received the intended dose of entrectinib, and because efficacy endpoints were defined in the protocol. However, the company could not confirm the number of patients who received the intended dose within the small group with ROS1+ NSCLC, and so the ERG considered it unreliable to provide evidence in support of the clinical effectiveness for entrectinib in the population of interest to this STA, given its aim as a Phase I study, the range of doses assessed, and the small number of patients with ROS1+ NSCLC recruited.

4.2.1.3 STARTRK-2 (RXDX-101-02)

STARTRK-2 is an ongoing single-arm, open-label Phase II study designed to investigate the safety and efficacy of entrectinib at the selected 600 mg daily dose in patients with a range of locally advanced or metastatic NTRK+, ROS1+ or ALK+ solid tumours (including those with controlled asymptomatic CNS metastases). STARTRK-2 is being conducted Australia, Europe, Asia and the USA, and has so far recruited 207 patients. STARTRK-2 is the only entrectinib study to recruit patients with ROS1+ NSCLC in the UK and the company confirmed that, as of April 2018, six patients with ROS1+ NSCLC have been enrolled via two of three participating UK sites.

Like the Phase I studies, patients were not eligible for STARTRK-2 if they had an active infection, gastrointestinal (GI) disease, interstitial lung disease or fibrosis, ECOG performance status greater than 2 (indicating limited mobility and self-care). Patients were not eligible if they had received previous targeted treatment for genetic alterations (e.g. ROS1-inhibiting TKIs) but could have received any other anticancer therapies (Table 3). The company outline that patients were enrolled across multiple solid tumour 'baskets' that were planned to be analysed separately. Patients were also enrolled to non-evaluable baskets to provide broader access to treatment (CS pg. 22).

Patients enrolled in STARTRK-2 received entrectinib 600 mg once daily, which was given orally as three 200 mg capsules. The ERG notes a protocol amendment that allowed dose escalation to 800 mg daily for patients with brain metastases, [redacted]. Entrectinib was otherwise delivered as it is likely to be in clinical practice should it be approved for use in the NHS.

The primary and secondary efficacy endpoints of STARTRK-2 were also analysed for the company's integrated analysis of entrectinib. The primary outcome was ORR, including best overall response (BOR), based on blinded independent committee review (BICR) determinations with RECIST v1.1. Tumour scans were evaluated prospectively in STARTRK-2 and the same team assessed scans retrospectively for patients in ALKA and STARTRK-1 who were included in the integrated analysis. Sensitivity analyses of ORR and DoR based on investigator assessed (INV) scans were also conducted. Secondary efficacy endpoints included OS, PFS, DoR and measures of HRQoL. Sensitivity analyses were also performed for PFS to evaluate the impact of BICR assessment and the impact of censored patients on results (missing tumour assessment and for new non-protocol anti-cancer therapy).

The presence of CNS metastases at baseline was determined by the investigator for subgroup analyses of OS, PFS and ORR and DoR. Additional endpoints assessed in patients with CNS metastases at baseline confirmed by BICR were intracranial ORR, DoR and PFS.

The EORTC quality of life instruments and the EQ-5D instruments were used. Data were collected prior to any dosing of entrectinib or clinical activity on Day 1 of each monthly visit starting at Cycle 1 and at the end of treatment.

4.2.1.4 STARTRK-NG (RXDX-101-03)

STARTRK-NG is a Phase I/II, open-label dose escalation and expansion trial investigating the efficacy and safety of entrectinib in children, adolescents and young adults aged 2 to 21 years. Patients with recurrent or refractory solid tumours and primary CNS tumours, with or without TRK, ROS1, or ALK fusions, are eligible, but no patients with ROS1+ NSCLC are enrolled to date. The ERG agrees that it was not appropriate to include any patients from STARTRK-NG in the efficacy analyses for entrectinib that underpin the economic model. The study is included in a secondary pooled safety analysis which includes patients exposed to entrectinib in ALKA, STARTRK-1 and STARTRK-2 regardless of tumour type.

4.2.2 Quality assessment

The company conducted a quality assessment for the ROS1+ NSCLC integrated analyses of entrectinib (ALKA, STARTRK-1 and STARTRK-2 pooled analysis) using the Downs and Black checklist which the ERG has validated (Appendix 10.6).[43] In general, the ERG agrees with the company's quality

assessment although the ERG considers it important to highlight that single-arm studies are considered low quality evidence and as discussed in Section 3.1 the ERG is concerned by the 12-month minimum follow-up restriction applied to patients included in the integrated analysis. The ERG agreed that pooling patients with ROS1+ NSCLC across the Phase I and II studies would increase the number of patients included in the integrated analysis but considered results of STARTRK-2 preferable because it was the only study that gave entrectinib at only the correct 600 mg starting dose. However, the ERG considers the 12-month minimum follow-up restriction to be a source of selection bias and that patients with no events during shorter follow-ups can also contribute useful information for key survival outcomes (OS and PFS) up to the point of being censored.

Other differences or areas the ERG considers it important to highlight from the quality assessment of the integrated analysis are:

- The dosing of entrectinib in ALKA and STARTRK-1 was not clear;
- The adverse events data were not reported for the integrated analysis, instead a more comprehensive data set was reported in the CS and this included patients with no follow-up restriction and from a fourth study (STARTRK-NG);
- The same third-party vendor, using the same group of independent readers and equivalent Imaging Charters was used for the BICR assessment of ORR and PFS although this was done retrospectively for ALKA and STARTRK-1 (and prospectively in STARTRK-2);
- The power calculation was based on ORR and so the integrated analysis was not necessarily powered for OS or PFS.

The company also conducted a quality assessment of studies that were used for the indirect comparisons of entrectinib with crizotinib (PROFILE 1001), PEM+PLAT (ASCEND-4) and chemotherapy (PROFILE 1007) in Appendix D.1 of their submission (Tables 26 and 27; not reproduced). The ERG does not consider chemotherapy a relevant comparator but presents a description and critique of PROFILE 1001 and ASCEND-4 in Section 4.4.1.

4.2.3 Baseline characteristics

Baseline characteristics for the company's primary efficacy set for the integrated analysis (n = 53) and the ERG's primary efficacy set for STARTRK-2 (n = 78) are provided in Appendix 10.2 (Table 55). Baseline characteristics for patients included in the company's integrated analysis from ALKA (n = 9), STARTRK-1 (n = 7) and STARTRK-2 (n = 37) are available in CS, Table 5. The company's primary efficacy set includes patients with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline who had at least 12 months' follow-up in ALKA, STARTRK-1 and STARTRK-2, regardless

of entrectinib dose. The ERG's efficacy set includes patients with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline who received entrectinib 600 mg (which could only be confirmed for STARTRK-2), irrespective of length of follow-up.

The ERG's clinical experts reviewed baseline characteristics for the company's primary ROS1+ NSCLC efficacy set and each study individually and considered them representative of patients with ROS1+ NSCLC in the UK. Mean age was 53.5 years (range 46 to 61) for the company's primary efficacy set and 53.3 years (range 28 to 86) in the ERG's preferred efficacy set, reflecting the younger age group who tend to be affected with ROS1+ NSCLC; over three quarters of both efficacy sets were under 65 (Table 55). Both efficacy sets include more females than males (64.2% and 62.8% for the company's and ERG's efficacy set, respectively) and just under half had a history of smoking (41.5% and 43.6%, respectively). Neither efficacy set is representative of the distribution of races in the UK population, but the ERG's efficacy set includes a smaller proportion of white patients (44.9% vs 58.5%) and a larger proportion of Asian patients (46.2% vs 35.8%) compared with the company's efficacy set; however, race is not known to affect disease course in ROS1+ NSCLC or response to treatment.

Regarding disease characteristics, approximately a third of patients had ECOG performance status of 0 and half had a performance status of 1 at baseline, which was true for the company's and the ERG's efficacy sets (Table 55). In general, younger age and good performance status is associated with better general health and ability to tolerate adverse effects of treatment, so similarity of the populations in these respects suggests that the company's and the ERG's efficacy sets are comparable. Nearly all patients had adenocarcinoma histology in the ERG's efficacy set (97.4%), whereas nearly a quarter of patients in the company's efficacy set had other tumour histologies, reflecting differences between STARTRK-2 and the Phase I studies. Mean time since diagnosis was 21 months in both efficacy sets, although the medians differed, and while most patients in both populations had stage IV disease at diagnosis, there was a higher proportion in the ERG's efficacy set than the company's (73.1 vs 61.4%). Moreover, nearly all patients had metastatic disease at study baseline (>94% in both efficacy sets). There were some differences between efficacy sets in terms of metastatic sites, but a similar proportion had brain metastases at baseline which are known to have a significant impact on prognosis and quality of life; the high proportion of patients with brain metastases in the entrectinib studies (~44%) is in line with what is known about CNS progression in ROS1+ NSCLC.

Two thirds of patients in the company's efficacy set had received at least one prior systemic therapy before entrectinib and there appears to be a transcription error for the ERG's preferred efficacy set. Table 9 of the clarification response indicates that 73.1% had received any prior systemic therapy and 39.7% had received no prior systemic therapy, which gives a proportion of 60.3% who had received at least one. Nonetheless, most patients had received a range of treatments that would likely not be given in the UK, so the effectiveness of entrectinib for untreated ROS1+ NSCLC in the NHS is likely to be

underestimates. Patients who had received prior ROS1-targeted therapy were not included in the analysis, but the company confirmed that around 10% had received other TKIs (company response to clarification), which was investigated as a treatment effect modifier. Information about the type of prior therapies received by patients in the ERG's preferred efficacy set was provided by the company at the clarification stage (see Appendix 10.4), which shows the most common prior therapies to be platinum compounds ([redacted]), pemetrexed ([redacted]), monoclonal antibodies ([redacted]), taxanes ([redacted]), gemcitabine or other pyrimidine analogues ([redacted]), and TKIs ([redacted]). Prior therapies received in the entrectinib studies are compared with those received in studies used to conduct MAICs with crizotinib and PEM+PLAT in Section 4.4.

4.2.4 Description and critique of statistical approach used

The company provided details of their statistical approach to the integrated analysis in Section B.2.4 of their submission, which is summarised with additional information from the ERG in Table 4.

Analysis of efficacy and safety endpoints were prespecified for baskets of patients with different tumour types in the three entrectinib studies, including analyses of patients with ROS1+ NSCLC. The sample size calculation for the company's integrated analysis of the ROS1+ NSCLC baskets in ALKA, STARTRK-1 and STARTRK-2 was based on an assumption of 70% response for the primary ORR by BICR endpoint. The company outline that a sample size of at least 50 patients would yield a 95% 2-sided confidence interval with precision of ±17% to exclude a lower limit of 50% (which would indicate a clinically meaningful response). The assumptions made are not justified with clinical opinion or evidence and, while the ERG appreciates that ORR was the protocol-defined primary outcome for the analysis, the trials were not designed to detect meaningful effects for key survival outcomes (OS and PFS).

Table 4. Summary of the company's statistical approach

Analysis	CS Section	Summary and additional information from the ERG
Sample size calculation	CS, Table 6	Assumed a true ORR by BICR of 70%, a sample size of at least 50 patients will yield a 95% 2-sided CI with precision ±17% that will exclude a lower limit of 50%. A response rate that excludes 50% or higher is considered clinically meaningful.
Efficacy analysis	CS, Section B.2 4	Single-arm, non-comparative data for event rates reported with 95% 2-sided CI using the Clopper-Pearson method. No formal significance tests performed and no statistical adjustments for multiplicity or subgroup effects of pooling studies (company justify with rarity of population and size of expected clinical benefit). Median OS, PFS and DOR estimated using Kaplan–Meier methods. ROS1+ NSCLC subset from mixed diagnosis studies defined in various ways: *1) Prespecified primary ROS1 efficacy set (n = 53; basis of the CS)*: ROS1-positive, ROS1 inhibitor naive NSCLC, measurable disease at baseline (RECIST v1.1), ≥12 months follow-up from onset of response or treatment discontinuation at 31 May 2018 CCOD) – analysis performed when 53 patients met the criteria. *2) Secondary ROS1 efficacy set (n = 94)*: primary efficacy set without 12 months follow-up restriction. *3) Post-hoc ERG efficacy set (n = 78)*: secondary efficacy set limited to patients who received the indicated dose (could only be confirmed for STARTRK-2).

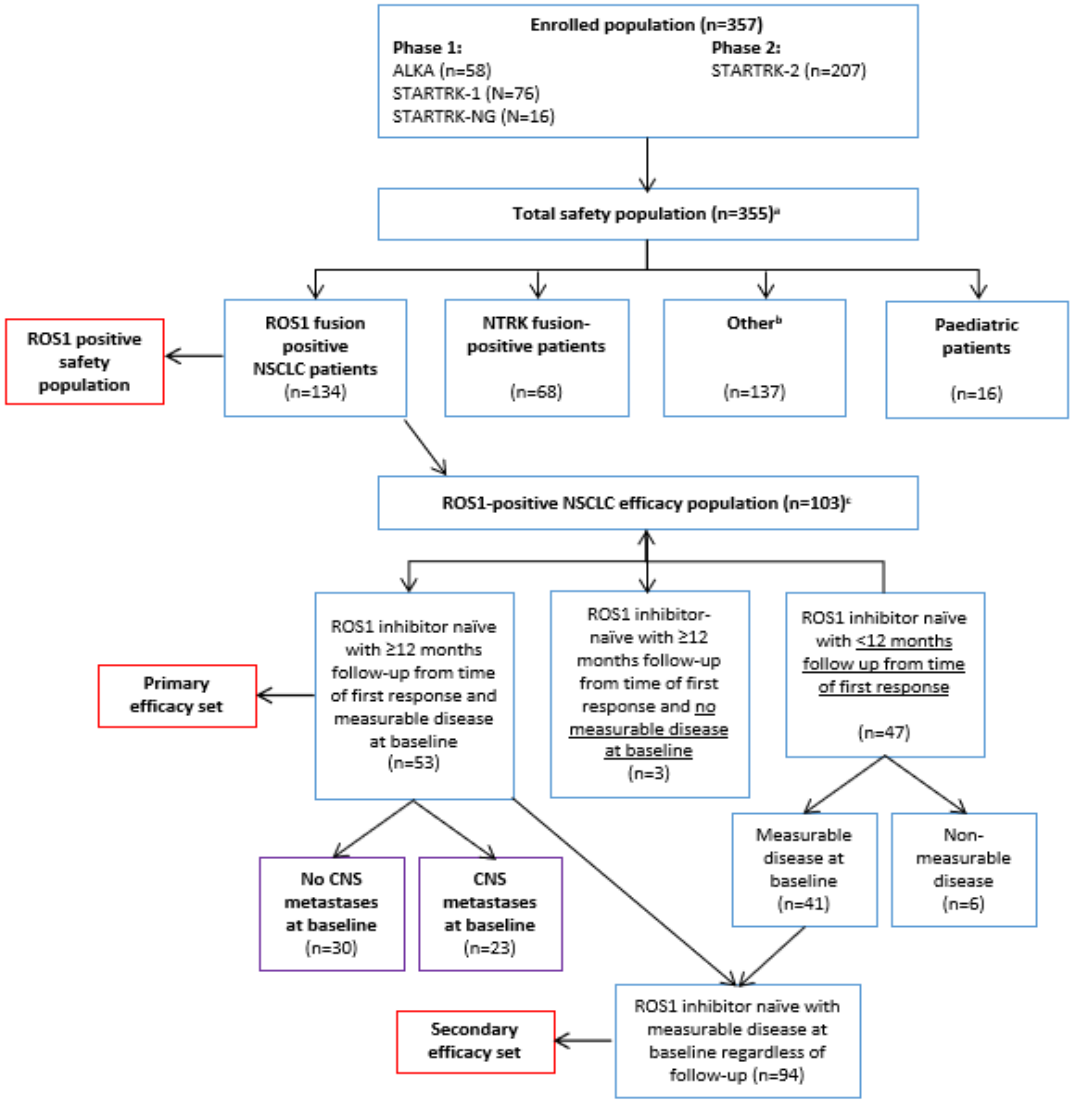
Safety analysis	CS pg. 33	All adverse reactions reported as percentage of patients experiencing at least one event. Common adverse events and treatment-related AEs limited to those reported in ≥10% of patients; Grade 3+ AEs and SAEs limited to those reported in ≥2% of patients Two datasets available from mixed diagnosis studies: *ROS1 safety population*: all ROS1+ NSCLC patients who received ≥ 1 dose. *Total safety population*: all entrectinib-treated patients across the trial programme
Approach to missing data	CS, Table 6	OS: Patients alive at the time of analysis or lost to follow-up/withdrew consent were censored on the last date they were known to be alive. Patients with no post-baseline information were censored at the time of first entrectinib dose. PFS and DOR: Patients without documented PD or death were censored at the last scan or, for PFS, at first dose if no baseline tumour assessment. ORR and BoR: patients with no post-baseline scan were deemed non-responders Approach to missing data for patient reported outcomes not specified.
Subgroup analysis	CS pg. 35; Appendix E	Prespecified subgroup analyses of efficacy endpoints by presence of CNS metastases at baseline, and a range of additional subgroup analyses ORR only.

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CCOD, clinical cut-off date; CI, confidence interval; CNS, central nervous system; DOR, duration of response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, response evaluation criteria for solid tumours.

The ERG considers the basic approach to analysing and presenting the single-arm data for each study and the integrated analysis appropriate to the study design and rarity of ROS1+ NSCLC. Briefly, the Clopper–Pearson method was used to calculate 95% 2-sided CI to give an estimate of precision for event probabilities, and the Kaplan–Meier method was used to calculate medians for time-to-event outcomes (OS, OFS, DOR). Subgroup analyses were conducted to explore OS, PFS and response rates for patients with and without CNS metastases at baseline. Other prespecified subgroup analyses were planned within the ROS1+ NSCLC primary efficacy set for ORR only, which were not listed in the NICE final scope. A further *post hoc* subgroup analysis to explore the possible impact of prior TKI use was requested by the ERG at the clarification stage on the advice of clinical experts.

As already described, the ERG's main concern with the entrectinib analyses presented by the company was the way the primary efficacy set had been defined to include patients regardless of entrectinib dose and exclude patients with follow-up shorter than 12 months (see Table 4 for definition). The prespecified efficacy and safety sets are illustrated in Figure 2 which illustrate the large number of patients excluded when the follow-up restriction is applied (details of patient flow broken down by study were provided by the company at the clarification stage and are provided in Appendix 10.7). At the clarification stage, the ERG set out a preferred efficacy set removing the follow-up restriction and focusing on patients who received entrectinib in line with its proposed marketing authorisation (see Section 3.1 and Section 4.2.1), for which all endpoints and subgroup results were subsequently provided. The company highlights that their integrated analysis was prespecified in agreement with the FDA, whereas the ERG's preferred analysis is *post hoc*. [redacted]

Figure 2. Entrectinib patient populations and analysis sets (reproduced from CS, Figure 2)



Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer.
Notes: a, excludes patients who did not receive entrectinib (n=2); b, includes ROS1-positive non-NSCLC, ALK fusion-positive and no gene fusion patients; c, excludes patients who received prior ROS1 inhibitor (n=27), ECOG PS>2 (n=3) and ROS1 biomarker ineligibility (n=1).

The company outline a standard approach to censoring in the analysis of OS, PFS and DoR (Table 4) but the heavy censoring required in the analysis of OS and PFS means the extrapolation required for the economic model are very uncertain (CS, pg. 116 and 182). A similar proportion of events were observed in the ERG's and the company's preferred analyses of OS and PFS, but the ERG considers it more informative to include eligible patients and censor where necessary than to exclude patients from the analysis altogether on the basis of an arbitrary minimum follow-up. A summary of patient status within the ERG's preferred efficacy set was provided by the company at clarification, which illustrates the level of censoring required for OS and PFS (Table 5).

Table 5. Summary of patient status for ERG efficacy set (n = 78) at 30 October 2018 (adapted from clarification response, Table 7)

Patient status				N (%)
On treatment	Censored for PFS	On Study	Censored for OS	[redacted]
	Progressed	On Study	Censored for OS	[redacted]
Completed treatment	Progressed	Discontinued Study	Died	[redacted]
	Progressed	On Study	Censored for OS	[redacted]
	Censored for PFS	On Study	Censored for OS	[redacted]
	Progressed	Discontinued Study	Censored for OS	[redacted]
	Censored for PFS	Discontinued Study	Censored for OS	[redacted]

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

Two clinical cut-off dates were reported in the submission for the company's preferred efficacy set (n = 53), of which the earlier of the two was used for the company's main analyses (see Table 6). The ERG asked for their preferred efficacy set to include data up to the later data-cut, but the company's response suggests that they do not have access to the required data with no restriction on follow-up. There was a lack of clarity in the way the data-cuts were described with regard to the cut-off dates for patient enrolment and the associated database lock, but the ERG understands that the data provided for its preferred efficacy set include patients enrolled up to the earlier enrolment cut-off (May 2018) with a database lock of 30 October 2018, rather than an enrolment cut-off of 30 October 2018 and database lock of December 2018 (Table 6). [redacted] (CQ response to Question A3).

Table 6. Data-cuts for the entrectinib analyses

Population	Cut-off for patient enrolment	Database lock	ERG comment
Company preferred efficacy set Integrated analysis with 12-month follow-up restriction	31 May 2018	31 July 2018	Company base case
	30 October 2018	21 December 2018	Clinical data presented in CS
ERG preferred efficacy set STARTRK-2 600 mg data with no follow-up restriction	31 May 2018	30 October 2018	ERG base case
	30 October 2018	Not stated	Not available

Abbreviations: ERG, evidence review group
Dates from CS page 35, and company response to clarification Question A3, page 11.

4.2.5 Summary statement

Clinical effectiveness evidence supporting the use of entrectinib for patients with ROS1+ NSCLC is available from three ongoing, mixed population, single-arm, open label studies – ALKA (n = 58; Italy), STARTRK-1 (n = 76; USA, South Korea and Spain) and STARTRK-2 (n = 207; Australia, Europe, Asia and the USA). ALKA and STARTRK-1 are Phase I dose-ranging studies that had a primary aim to identify dose-limiting toxicities and the maximum tolerated dose of entrectinib, and STARTRK-2 is a Phase II study designed to study the safety and efficacy of entrectinib within its proposed marketing

authorisation. All three studies are recruiting mixed populations of patients with locally advanced or metastatic solid tumours testing positive for ROS1, ALK, or NTRK1/2/3 genetic alterations.

The company's primary efficacy analyses are based on an integrated analysis of patients from all three studies with ROS1-inhibitor naïve ROS1+ NSCLC, measurable disease at baseline, and at least 12 months' follow-up from first response (n = 53). The safety population includes all patients with ROS1+ NSCLC ([redacted]) from the three studies and a fourth paediatric study, STARTRK-NG, although no patients with ROS1+ NSCLC have yet been recruited. The primary and secondary efficacy endpoints of STARTRK-2 formed the basis of the company's integrated analysis of entrectinib, namely ORR (primary outcome), OS, PFS, DoR and HRQoL (including generic, cancer, and lung cancer specific measures).

The ERG's preferred efficacy set includes 78 patients from STARTRK-2 with ROS1-inhibitor naïve ROS1+ NSCLC who received entrectinib in line with its intended marketing authorisation. The ERG preferred the efficacy set to be limited to patients who received the recommended 600 mg starting dose of entrectinib, which could only be confirmed for STARTRK-2, and for there to be no minimum follow-up applied ([redacted] patients had been excluded for this reason). Patients with no events during shorter follow-ups contribute survival data up to the point at which they are censored. The company use the earlier of two clinical cut-off dates for their primary analyses of their preferred efficacy set (31 May 2018) and, while the ERG asked for their preferred efficacy set to be analysed up to the later data-cut (31 October 2018), the company's response suggests that they do not yet have access to the required data.

The ERG and company preferred analyses of entrectinib are based on single-arm data and are therefore considered low quality evidence. The 12-month minimum follow-up restriction to define the primary efficacy set for the integrated analysis may introduce selection bias, and the ERG considers its primary efficacy set more reliable for decision-making. STARTRK-2 is likely to be the most robust study because it recruited the largest population and is the only study for which dosing could be confirmed. STARTRK-2 is also the only study designed to assess safety and efficacy endpoints including HRQoL and it is the only study to use prospective BICR assessment of tumour scans (BICR assessment was done retrospectively for the small number of patients included in the integrated analysis from ALKA and STARTRK-1).

The ERG considers the basic approach to analysing and presenting the single-arm data for each study and the integrated analysis appropriate to the study design and rarity of ROS1+ NSCLC. Subgroup analyses were conducted to explore OS, PFS and response rates for patients with and without CNS metastases at baseline and a *post hoc* subgroup analysis was provided at the request of the ERG to explore the possible impact of prior TKI use. The company's approach to censoring for OS and PFS was appropriate but the heavy censoring required for OS in particular introduces uncertainty in the

extrapolation required for the economic model. The ERG notes that the power calculation for the company's integrated analysis was based on ORR and so the company's primary efficacy set for the integrated analysis was not necessarily powered for OS or PFS.

The company propose that entrectinib will be used at first- or second-line for patients with ROS1+ NSCLC. The ERG's clinical experts agreed that crizotinib (only available through the CDF) and pemetrexed plus platinum therapy (PEM+PLAT) are the relevant comparators for entrectinib, and all other comparators listed in the NICE final scope would be used later in the treatment pathway (Section 3.3). The entrectinib studies provide no comparative data and so SLRs were carried out by the company to identify studies with which to conduct indirect treatment comparisons:

- PROFILE 1001 – a Phase I single-arm study of crizotinib in an ROS1+ NSCLC – was chosen to support an MAIC of entrectinib versus crizotinib;

- ASCEND-4 – a Phase III RCT of ceritinib versus PEM+PLAT (with pemetrexed maintenance therapy) for untreated ALK+ NSCLC – was chosen to inform an MAIC of entrectinib versus PEM+PLAT because there were no studies in an ROS1+ NSCLC. However, the company do not use the ASCEND-4 MAIC to estimate relative treatment effects in the economic model, and instead apply hazard ratios for crizotinib versus PEM+PLAT from PROFILE 1014 to the results from the entrectinib versus crizotinib MAIC (Section 4.4).

The ERG is satisfied that the company's searches identified all relevant evidence to inform the decision problem. Alternative sources of evidence for crizotinib in a ROS1+ NSCLC were identified (e.g. AcSe, EUROS, OxOnc),[41, 42, 44] but the ERG's clinical experts agree that PROFILE 1001 is the most robust evidence for crizotinib in a ROS1+ NSCLC population. ASCEND-4 was chosen for the PEM+PLAT comparison because no other studies gave pemetrexed maintenance therapy, which most patients receive in UK clinical practice. The ERG considers that, while other studies may have benefits over ASCEND-4 for the PEM+PLAT comparison (e.g. length of follow-up, sample size, study quality), all comparisons would be limited by reliance on the assumption of similarity between the ALK+ and ROS1+ NSCLC populations. The ERG considers there to be no consensus regarding the use of evidence from ALK+ populations as a proxy for ROS1+ NSCLC, and summarises the arguments as follows:

- The two populations are demographically similar (younger age than NSCLC in general, higher proportion of non-smokers, primarily adenocarcinoma histology), treatments are comparable, and the kinases of ROS1 and ALK share 77% of amino acids (ERG clinical experts and TA529);

- PFS was longer with crizotinib in PROFILE 1001 (ROS1+ NSCLC) than in PROFILE 1014 and PROFILE 1007 (ALK+NSCLC), but ROS1 fusions are rare and naïve comparisons may be are confounded by baseline differences and prior treatments.

- The appraisal committee for TA529 considered the use of evidence from patients with ALK+ NSCLC, "very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals";

The company and the ERG preferred efficacy sets for the entrectinib analyses are considered representative of patients with ROS1+ NSCLC in the UK (mean age ~53 years, ~60% female, ~90% ECOG PS 0 or 1 and ~40% with a history of smoking). The proportion of Asian patients is higher in the ERG preferred efficacy set (46.2%) than the company's efficacy set (35.8%), and both are higher than in the UK, but race is not known to affect disease course or response to treatment in ROS1+ NSCLC. Baseline characteristics are mostly comparable between the company and ERG preferred efficacy sets but the ERG's preferred efficacy set more often had adenocarcinoma (97.4 vs 76.1%) and a higher proportion had Stage IV disease (73.1 vs 61.4%), but nearly all patients had metastatic disease at study baseline (>94%) and a similar proportion had brain metastases (~44%), which have an important impact on prognosis and quality of life. Approximately two thirds of the company and the ERG efficacy sets for the analyses of entrectinib had received at least one prior systemic therapy before entrectinib (~70%), some of which are not available in the UK, meaning the effectiveness of entrectinib for untreated ROS1+ NSCLC may be underestimated.

The company took an 'all lines' approach in its indirect treatment comparisons with crizotinib and PEM+PLAT because there were too few patients with ROS1+ NSCLC in the entrectinib studies to conduct separate analyses by line of treatment. The MAICs conducted by the company adjusted for key differences in baseline characteristics and prior therapies between the entrectinib populations and patients in PROFILE 1001 and ASCEND-4, which is discussed in Section 4.4.

4.3 Clinical effectiveness results

For each of the endpoints listed in final scope, results are presented for the company's primary efficacy set (n = 53) and the ERG's preferred efficacy set provided by the company at the clarification stage. The ERG has not reproduced results for patients in each study that contributed to the integrated analysis presented by the company. For clarify, three sets of results are available across the two efficacy sets, which are defined as follows:

Company's primary efficacy set (integrated analysis, n = 53): all patients in ALKA, STARTRK-1 and STARTRK-2 with ROS1-inhibitor naïve ROS1+ NSCLC, measurable disease at baseline, and at least 12 months' follow-up from first response, regardless of the dose of entrectinib received. Data are

available for the company's preferred CCOD including patients enrolled up to 31 May 2018 (with a 31 July 2018 database lock) and a later CCOD including patients enrolled up to 30 October 2018 (with a 21 December 2018 database lock).

ERG preferred efficacy set (n = 78): patients in STARTRK-2 (who all received entrectinib 600 mg in line with the proposed marketing authorisation) with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline irrespective of follow-up duration. Data are reported for a single CCOD including patients enrolled up to 31 May 2018 (with a database lock of October 2018).

4.3.1 Overall survival

Median OS was not estimable at primary CCOD of 31 May 2018 or at the later CCOD of 30 October 2018 for the company's primary efficacy set. At the time of the first analysis, after 15.5 months' follow-up, [redacted] patients had died ([redacted]), and a further [redacted] had died by the later analysis ([redacted]). Mean follow-up for the ERG's preferred analysis was [redacted] months (company response to clarification, Table 8), at which point [redacted] patients had died ([redacted]). Median OS for the ERG's preferred efficacy set was calculated as [redacted] months, but the data are unreliable due to the low proportion of patients having died, which is similar to the company's primary analysis. The ERG has not reproduced data that were only provided for the company's analyses indicating the number of patients remaining at risk and event-free probabilities at 6, 9, 12 and 18 months, which can be found in CS Table 11.

Table 7. Overall survival with entrectinib

	Company's integrated analysis (n = 53)		ERG's preferred analysis (n = 78)
CCOD for enrolment	**31 May 2018**	**30 Oct 2018**	**31 May 2018**
Mean months of follow-up (95% CI)	[redacted]	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CCOD, clinical cut-off date; CI, confidence interval; ERG, evidence review group; n, number of patients.
Data from CS Table 11 and company response to clarification Table 10.

Clinical experts consulted by the ERG and the company highlighted that recent real-world studies have shown substantially shorter OS and PFS than has been observed in clinical trials of ROS1+ NSCLC. The ERG assesses the clinical plausibility of OS observed in the entrectinib and comparator trials and the potential impact of subsequent therapies with results of the MAICs (Section 4.4). KM plots of OS from the company's and the ERG's preferred analyses are also presented with results of the MAICs that were conducted to provide comparative estimates of OS, PFS and ORR for entrectinib versus crizotinib and PEM+PLAT. The KM plots show OS before and after the entrectinib population was reweighted to more closely reflect the comparator study population (see Section 4.4).

4.3.2 Progression-free survival

At the primary efficacy analysis for the company's integrated analysis, median PFS by BICR was [redacted] months (95% CI: [redacted] months), which remained similar at the later 30 October 2018 CCOD (Table 8). However, median PFS for the ERG's preferred analysis is [redacted] at [redacted] months (95% CI [redacted]), and PFS for the company-defined secondary efficacy set (their primary efficacy set without a minimum follow-up) was [redacted] months (95% CI [redacted] months).

Table 8. Progression-free (BICR) with entrectinib

	Company's integrated analysis (n = 53)		ERG's preferred analysis (n = 78)
CCOD for enrolment	**31 May 2018**	**30 Oct 2018**	**31 May 2018**
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
First event progression	[redacted]	[redacted]	[redacted]
First event death	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CCOD, clinical cut-off date; CI, confidence interval; NE. not estimable.
Data from CS Table 9 and company response to clarification Table 10.

PFS in the entrectinib studies was also measured by investigators, although results were not submitted, and the ERG agrees with the company that PFS by BICR is the preferred endpoint. The company also conducted two sensitivity analyses for the PFS by BICR endpoint using different rules for censoring. The ERG agrees with the company that the sensitivity analyses censoring patients with missing tumour assessments (CS Appendix, Table 71) and censoring at the point of new non-protocol anti-cancer therapies (CS Appendix, Table 72) give very similar results to the company's primary analysis based on standard rules for PFS censoring (see Table 4).

As for OS, clinical experts consulted by the ERG and the company highlighted that recent real-world studies have shown substantially shorter PFS than has been observed in clinical trials of ROS1+ NSCLC. The ERG assesses the applicability of PFS observed in the entrectinib and comparator trials to patients in the UK with results of the MAICs. KM plots of PFS showing results of the company's and the ERG's preferred entrectinib analyses before and after reweighting are also presented with results of the MAICs (see Section 4.4).

The company outlined the BICR tumour scan assessment procedures for ORR in STARTRK-2 and the Phase I trials and the ERG is unclear whether the same procedure applies for PFS. Tumour scans were assessed prospectively in STARTRK-2 and retrospectively for patients included in the efficacy set from ALKA and STARTRK-1. If it does, the ERG's preferred efficacy may be more reliable because it only includes patients from STARTRK-2 whose scans would have been assessed in a prospective manner. The ERG considers prospective assessment of scans preferable because retrospective BICR assessments that are incongruous with an investigator's assessment can impact effectiveness, for example, if a

patient is taken off treatment at the point of investigator-assessed progression before the point of BICR progression or continued on treatment beyond the progression date later assessed by BICR.

4.3.3 Response rate

In the company's primary analysis of ORR by BICR (CCOD 31 May 2018), [redacted] of patients showed a complete ([redacted]) or partial response ([redacted]) to treatment (repeat scans show durability of at least 28 days from first response; Table 9), and median duration of response was [redacted] months, 95% CI: [redacted]). Clinical benefit rate (CBR) is [redacted] ORR in the company's analysis because [redacted] patients had stable disease for at least 6 months, and the definition was otherwise the same. ORR by BICR was slightly [redacted] in the ERG's preferred analysis than the company's analysis at [redacted] and median duration of response was [redacted] ([redacted] months; 95% CI [redacted]). ORR, along with OS and PFS was assessed in the MAICs conducted to provide a comparison of entrectinib with crizotinib and PEM+PLAT, which are discussed in Section 4.4.

Table 9. Tumour response with entrectinib (BICR; RECIST v1.1)

	Company's integrated analysis (n = 53)		ERG's preferred analysis (n = 78)
CCOD for enrolment	**31 May 2018**	**30 Oct 2018**	**30 Oct 2018**
Objective response (CR or PR confirmed at repeat readings at least 28 days apart)			
Patients with response, n (%)	[redacted]	[redacted]	[redacted]
95% CI for response	[redacted]	[redacted]	[redacted]
Best objective response rate, n (%)			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease[a]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Non-complete or partial response[a,b]	[redacted]	[redacted]	[redacted]
Missing or unevaluable[c]	[redacted]	[redacted]	[redacted]
Clinical benefit rate (CR or PR plus patients with SD for ≥ 6 months after starting entrectinib)			
Patients with events, n (%)	[redacted]	[redacted]	[redacted]
95% CI for clinical benefit rate	[redacted]	[redacted]	[redacted]
Duration of response[d]			
Median months (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CCOD, clinical cut-off date; CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response.
Data from CS Table 7 and company response to clarification Table 10.
Notes: a, SD and Non-CR/Non-PD must be observed study day 35 or later, otherwise they count as NE; b, Patients were categorised as having Non CR/PD if they had non-target lesions (as assessed by BICR), but had measurable disease at baseline as assessed by Investigator; c, Missing or unevaluable category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response; d, estimated using KM methods and measures of time from first response to death or progressive disease (censored at the last tumour assessment); CIs are calculated using the Clopper-Pearson method.

The ERG accepts that removing the minimum follow-up restriction means that DOR is likely to be more stable in the company's preferred analysis but considers the ERG's analysis preferable for other efficacy outcomes reflected in the economic model (OS and PFS). The KM plot of DoR by BICR for the [redacted]

patients who had a partial or complete response in the company's preferred analysis (CCOD 31 May 2018) is shown in Figure 3.

Figure 3. Duration of response (BICR) for the company's primary analysis (reproduced from CS Figure 3)

Abbreviations: BICR, blinded independent central review; CCOD, clinical cut-off date; CI, confidence interval; CS, company's submission; DBL, database lock; NSCLC, non-small cell lung cancer.

The ERG notes that tumour scans were evaluated prospectively in STARTRK-2 and scans of patients included in the company's primary efficacy set from ALKA and STARTRK-1 were evaluated retrospectively by the same BICR team as STARTRK-2 using equivalent Imaging Review Charters (see Section 4.2.1 and CS, pg. 27). The company presented sensitivity analyses for response as assessed by investigators in CS Appendix L.3, but the ERG agrees with the company that response by BICR is the preferred endpoint.

4.3.4 Potential benefits for CNS disease

Time to CNS progression (including all patients regardless of baseline CNS disease), intracranial PFS (including only patients with CNS metastases at baseline) and intracranial response were not listed in the NICE final scope, but results were presented in the submission in support of the proposed benefit of entrectinib over existing treatments for CNS disease. The ERG's clinical experts expect entrectinib to show such a benefit in clinical practice because it is CNS-active, but none of the CNS outcomes are included in the MAICs conducted to compare entrectinib with crizotinib or PEM+PLAT, so there is currently no comparative clinical evidence to support the assumption. The ERG has included the single-arm evidence from the entrectinib trials as an appendix in light of the profound impact of CNS metastases on quality of life described by clinical experts (Appendix 10.8, Table 69).

4.3.5 Time to treatment discontinuation

Time to treatment discontinuation (TTD), also referred to as time on treatment (ToT), is listed as an outcome for all three entrectinib studies (CS, Table 3), but the data were not presented with the clinical effectiveness results. ToT data for entrectinib were used to estimate treatment costs for the economic model (CS, page 104), based on the company's and the ERG's preferred efficacy sets, and survival curves were fitted to each data set to extrapolate beyond the trial data (CS, Section B.3.3.2). A critique of the company's assumptions about time to treatment discontinuation and the methods used to calculate TTD for the comparators is critiqued in Section 5.3.5.

4.3.6 Health-related quality of life

Patient reported outcome (PRO) data for entrectinib are only available from the STARTRK-2 study, because they were not measured in the Phase I trials. Results for the EORTC-QLQ-30,[38] a generic cancer quality of life measure, and the lung cancer specific QLQ-LC13[39] module are provided in Appendix 10.8 as they are not reflected in the economic model. Results for the EQ-5D are covered in Section 5.3.7.

4.3.7 Subgroup analyses

The company provided results for key efficacy outcomes separately for patients with and without CNS disease at baseline, as listed in the NICE final scope, but the subgroups are not reflected in the economic model. Results suggest that PFS is likely to be [redacted] and response rates [redacted] for patients with CNS disease than those without CNS disease at baseline (Appendix 10.9) and differences were more pronounced between subgroup for PFS and DOR in the company's preferred analysis (PFS [redacted] versus [redacted] months; DoR [redacted] versus [redacted] months) than ERG's preferred analyses. The ERG highlights that all subgroup analyses are based on small numbers of events and, for OS, immature survival follow-up.

Results for the prior TKI subgroup analysis requested by the ERG at the clarification stage do not suggest an important difference between subgroups (Appendix 10.9).

4.3.8 Safety data

Adverse event data for entrectinib were submitted for the ROS1 safety set ([redacted] patients with ROS1+ NSCLC who had received at least one dose of entrectinib in ALKA, STARTRK-1 and STARTRK-2) and the total safety set (n=[redacted]; any patient who received any dose of entrectinib in STARTRK-NG, ALKA, STARTRK-1 and STARTRK-2), but the company used data for their preferred efficacy set to reflect selected Grade 3 and 4 events in the economic model (see Section 5.3.6). The ERG provides a critique of the adverse event data for the ROS1 safety set and total safety set in Appendix 10.10.

Briefly, [redacted] of patients in the ROS1+ safety set experienced at least one AE and [redacted] of patients were deemed to have a treatment-related AE. Treatment-related Grade 3 or higher AEs occurred in [redacted] of the ROS1+ patients and treatment-related SAEs in [redacted]% of patients. The most frequently reported treatment related AEs in the ROS1+ population were dysgeusia ([redacted]%), dizziness ([redacted]%), constipation ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), and fatigue ([redacted]%). AEs led to dose interruption in [redacted] and dose reduction in [redacted] of ROS1+ patients (see Appendix 10.10).

4.4 Critique of the matched adjusted indirect comparisons (MAICs)

The company provide MAICs to compare entrectinib with crizotinib and PEM+PLAT, the two comparators addressed in the economic model and considered most relevant by the ERG's clinical experts (Section 3.3). The ERG has not provided a critique of a third MAIC presented in the company's appendix to provide estimates for entrectinib versus docetaxel using PROFILE 1007 (CS, Appendix D.4), because based on feedback from clinical experts, the ERG agrees with the company that it is not a relevant comparator for this appraisal.

4.4.1 Critique of trials identified and included in the MAIC

As discussed in Section 4.1, the ERG is satisfied that PROFILE 1001 is the most robust study available of crizotinib for ROS1+ NSCLC to provide a comparison with entrectinib. ASCEND-4 was chosen to provide the PEM+PLAT comparison because it was the only study to give pemetrexed maintenance therapy, which is considered standard practice in the UK. While the ERG does not consider there to have been full consideration of the pros and cons of alternative studies for the PEM+PLAT comparison, all options are subject to the same uncertainties of using an ALK+ population as a proxy for ROS1+ NSCLC. Details of PROFILE 1001 and ASCEND-4 as well as the alternative studies considered by the company in their feasibility assessment for both MAICs are summarised in Appendix 10.5 along with the company's reasoning for choosing PROFILE 1001 and ASCEND-4.

It should be noted that the MAIC conducted with ASCEND-4 for the entrectinib versus PEM+PLAT comparison was not the method chosen to derive estimates for PEM+PLAT in the economic model, although it was used as a scenario analysis. The company instead derive PEM+PLAT estimates by applying hazard ratios from PROFILE 1014 – an RCT comparing crizotinib with PEM+PLAT without pemetrexed maintenance for ALK+ NSCLC – to the ROS1-specific results of the entrectinib versus crizotinib MAIC. The company's alternative approach is described afterwards in Section 4.4.1.2.1, and critiqued further in the review of cost-effectiveness (Section 5.3.5).

4.4.1.1 PROFILE 1001 – study chosen to make comparison with crizotinib

PROFILE 1001 is a multicentre, Phase I, open-label, single arm study of crizotinib in patients with locally advanced or metastatic ROS1+ NSCLC. The ERG notes that, like the entrectinib STARTRK-1

study, PROFILE 1001 included an initial dose-escalation phase to establish the maximum dose of crizotinib followed by a longer-term dose expansion to further investigate efficacy and safety. Like the evidence base for entrectinib in ROS1+ NSCLC presented by the company, PROFILE 1001 included a mixed population of treatment-naïve and pre-treated patients. The company's quality assessment of PROFILE 1001 is reproduced with the Downs and Black quality assessment of the entrectinib integrated analysis in Appendix 10.6. The ERG considers PROFILE 1001 to be of similar quality to the entrectinib evidence and subject to the same limitations pertaining to single-arm studies (see Section 4.2.2).

The primary outcome in PROFILE 1001 was ORR, but unlike the entrectinib studies, there is no description in the publications of whether assessments were made by investigators or BICR. The ERG notes from the committee papers for TA529, for which PROFILE 1001 was the primary evidence source, that, "assessments of tumour response and disease progression were made by IRR" where IRR stands for independent radiology review (page 53) and, "assessors carrying out the IRR were blinded to outside radiology reports and investigator assessments" (page 53).[36]

The primary outcomes for PROFILE 1001 were reported in 2014 by which point 50 patients had been recruited, and the most recent results are for 53 patients with a median follow-up of 63 months (compared with 15.5 months for the company's primary integrated analysis of entrectinib).

The company do not present a detailed comparison of the trials to assess similarity in their designs and populations to support the MAIC. The ERG could find only limited baseline characteristics for the PROFILE 1001 population, even after consulting the committee papers for TA529, and notes that data are not available to match the entrectinib population for disease stage at diagnosis, time since diagnosis, disease stage at baseline, or the proportion of patients who had CNS metastases at baseline. Disease stage at baseline and the presence of CNS metastases at baseline are important treatment effect modifiers and not accounting for potential differences in these characteristics will introduce bias into the MAIC.

High level data about the type of prior therapies received by patients before crizotinib in PROFILE 1001 are available in the supplementary materials for the main publication of PROFILE 1001 (Shaw 2014[45]), which are shown together with prior therapy data for the ERG's preferred efficacy set for entrectinib in Appendix 10.3. In PROFILE 1001, 86% of the 50 patients for whom data were available had received at least one prior therapy, including platinum compounds (80%), pemetrexed (72%), taxanes (40%), TKIs (32%) bevacizumab (32%) and gemcitabine (22%) and vinorelbine (6%). The overall proportion of patients who received any prior therapy in the entrectinib studies is similar (86.8%; Table 55), but the proportions who received each of the main systemic therapies is consistently lower in the entrectinib studies than PROFILE 1001 (Table 56). The MAIC conducted by the company used the overall proportion of patients who had received prior therapy as a factor for matching, and the ERG's

clinical experts do not expect the differences in the types of systemic treatments received to introduce important bias.

4.4.1.2 ASCEND-4 – study chosen to make comparison with PEM+PLAT

The MAIC of entrectinib versus PEM+PLAT uses evidence from the PEM+PLAT group (n = 187) of ASCEND-4, a large multicentre, Phase III, open-label, randomised controlled trial of ceritinib versus PEM+PLAT and pemetrexed maintenance in patients with locally advanced or metastatic ALK+ NSCLC. The study was well conducted and measured all key outcomes systematically, including the assessment of PFS and ORR by BICR, and median follow-up is at least 33 months (CS, Table 16). The company conducted a quality assessment of ASCEND-4 which found the study to be low risk of bias across all domains (CS Appendix D.1, Table 27).

As outlined in Section 4.1, the ERG accepts that no evidence exists for PEM+PLAT in a ROS1+ NSCLC population but is aware of conflicting arguments regarding the appropriateness of using data for an ALK+ NSCLC population. The fusions are biologically similar, various clinical experts advising during the NICE appraisal of crizotinib for ROS1+ NSCLC (TA529)[12] considered the populations comparable and the EMA accepted the assumption that ALK+ NSCLC was generalisable to ROS1+ NSCLC. Experts have expressed different opinions regarding the relative effectiveness of crizotinib for ALK+ and ROS1+ NSCLC and, while studies of crizotinib for ROS1+NSCLC have shown longer PFS (19.3 months in PROFILE 1001) than studies in ALK+ NSCLC (10.9 and 7.7 months for PROFILE 1014 and PROFILE 1007, respectively), these are naïve comparisons and the differences could be driven by other factors (e.g. disease burden or prior treatment of brain metastases).

The ERG considers there to be no robust evidence to support or oppose using an ALK+ population as a proxy for ROS1+ and therefore assesses results of the MAIC comparing entrectinib in a ROS1+ population to PEM+PLAT in an ALK+ NSCLC population with caution. Crucially, there is no way to quantify, and adjust if necessary, for differences in treatment effect that are attributable to the underlying gene fusion (ALK+ or ROS1+).

As for PROFILE 1001, the company do not present a detailed comparison of ASCEND-4 and the entrectinib studies but highlight two key issues that are likely to have an important impact on the estimates derived from the MAIC. Firstly, ASCEND-4 allowed treatment crossover upon progression and, at the time of analysis, 42.7% of patients who received PEM+PLAT (80/187) had crossed over to receive ceritinib, and 51.6% had received any subsequent ALK inhibitor (105/187),[70] so the survival benefit of PEM+PLAT is likely overestimated. Secondly, the study recruited only patients with untreated disease which, while in line with where the company are positioning entrectinib in the treatment pathway, introduces a key discrepancy between ASCEND-4 and patients receiving entrectinib. Given that only a small number of patients in the entrectinib studies were treatment naïve,

it was not possible to adjust on this basis, which may also overestimate the benefit of PEM+PLAT relative to entrectinib. However, baseline characteristics were otherwise available for matching and so differences between entrectinib and PEM+PLAT-treated patients that might be expected for patients at different stages in the treatment pathway – such as disease stage and performance status – could be adjusted for, as well as other factors highlighted by the ERG's clinical experts as prognostic.

4.4.1.2.1 PROFILE 1014 – study used to derive PEM+PLAT estimates for the economic model

Acknowledging the limitations of the MAIC with ASCEND-4, the company use an alternative method to derive estimates of OS and PFS for PEM+PLAT in the economic model using PROFILE 1014. PROFILE 1014 is a multicentre, open-label RCT that compared crizotinib to PEM+PLAT (without pemetrexed maintenance therapy) for patients with untreated ALK+ NSCLC. The study was open-label and patients randomised to receive PEM+PLAT were allowed to cross over to crizotinib after disease progression (see Table 58). The company apply HRs for OS and PFS from PROFILE 1014 to results of the entrectinib versus crizotinib MAIC with PROFILE 1001 to derive estimates for PEM+PLAT. The ERG accepts that this method retains the benefits of a randomised comparison and only assumes that the *relative* effect of crizotinib versus PEM+PLAT is similar for ALK+ and ROS1+ NSCLC populations. However, the ERG highlights the following key limitations in the application of HRs from PROFILE 1014 to derive treatment effects for PEM+PLAT:

- The company use a crossover-adjusted HR for OS from PROFILE 1014 that was calculated using a method deemed flawed by the appraisal committee for TA529. Unadjusted results were considered preferable for TA529 because only 19% of patients had crossed over;

- Assessments of proportional hazards for PROFILE 1014 in TA529 indicate that the assumption may be reasonable for adjusted and unadjusted OS but does not hold for PFS, so using HRs to estimate relative PFS between crizotinib and PEM+PLAT is likely to be flawed;

- PEM+PLAT was not delivered with pemetrexed maintenance in PROFILE 1014 as it is in ASCEND-4 and UK clinical practice, so the effectiveness of PEM+PLAT relative to crizotinib may be underestimated for patients in the UK;

- The appropriateness of applying HRs from PROFILE 1014 relies on the relative treatment effect of crizotinib versus PEM+PLAT in ALK+ NSCLC being the same for patients with ROS1+ NSCLC, which is unknown.

- More mature OS is now available for PROFILE 1014, however, in this later data set, 84% of patients have crossed over to crizotinib and so utilising the more mature unadjusted OS from this trial is no longer a robust option for estimating OS for PEM+PLAT.

4.4.2 Description and critique of the statistical approach used

The ERG reviewed the company's methods of conducting the MAICs and considers them appropriate. Justification was provided at the clarification stage regarding the choice of covariates for adjustment, which were constrained by limitations of the evidence base. Weighted patient characteristics for the company and ERG efficacy sets following the matching procedures suggest the population was matched successfully for the chosen characteristics to PROFILE 1001 and ASCEND-4 for each MAIC (full details provided in Appendix 0).

The ERG highlights the following issues and uncertainties which mostly relate to the limitations of the evidence:

- The company's MAIC with PROFILE 1001 (crizotinib) uses their primary integrated analysis of entrectinib at the 31 May 2018 CCOD. Data for the later CCOD including patients enrolled up to 30 October 2018 were available for the company's preferred efficacy set, but the company chose not to use the later data cut for their base case. Furthermore, updated data for PROFILE 1001 were not used for their base case (Shaw 2019).[46]

- The ERG's preferred PROFILE 1001 MAIC (crizotinib) is based on the ERG efficacy set for entrectinib (patients enrolled up to 31 May 2018 receiving 600mg dose of entrectinib with no minimum follow-up) and the longer follow-up data for crizotinib in PROFILE 1001 from Shaw 2019.

- The PROFILE 1001 MAICs (crizotinib) reweighted the entrectinib population (company or ERG efficacy set) according to the following population characteristics: sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, prior treatments (treatment naïve vs prior treatment), age. However, disease stage and the presence of CNS metastases were not available for PROFILE 1001 and are likely to be key effect modifiers which could not be included as covariates.

- The company conducted an alternative MAIC to compare entrectinib with crizotinib using a population of 69 patients meeting STARTRK-2 eligibility criteria from the US Flatiron Health Analytic Database. The company acknowledge limitations in the Flatiron dataset due to missing baseline and outcome data and varying follow-up times and the ERG considered there to be insufficient information about the population and analysis presented to assess the robustness of the Flatiron MAIC.

- The ASCEND-4 MAIC (PEM+PLAT) reweighted the entrectinib population (company or ERG efficacy set) according to the following population characteristics: sex, race (Asian vs. non-

Asian), ECOG (0 vs. 1 or 2), smoking history, age, and disease stage (stage IIIB vs stage IV non-CNS metastasis vs stage IV CNS metastasis). Histology was not included because it was not available for STARTRK-1 and, while the proportion of patients with adenocarcinoma in ASCEND-4 is [redacted] to the ERG's preferred efficacy set (93% and [redacted], respectively), the percentage with adenocarcinoma in the company's efficacy set is [redacted] ([redacted]).

- ASCEND-4 recruited a purely ALK+ population and there is no way to quantify, and if necessary adjust, for potential differences in treatment effect that are attributable to the underlying gene fusion (ALK+ or ROS1+). Furthermore, ASCEND-4 recruited a purely treatment-naïve population whereas most of the entrectinib-treated patients had received at least one prior therapy, which prevented matching on this basis.

- The method used to estimate PEM+PLAT in the economic model by applying HRs from PROFILE 1014 did not involve a matching procedure because it was not an MAIC.

4.4.3 Results for entrectinib versus crizotinib

4.4.3.1 Overall survival

The company's analysis suggests a [redacted] OS benefit of entrectinib versus crizotinib ([redacted]) than the ERG's preferred analysis ([redacted]). [redacted]

The inverse of the HR is applied to the extrapolated entrectinib OS curve to estimate the OS curve for crizotinib (see Section 5.3.5). Figure 4 is a KM plot of OS for entrectinib before and after reweighting compared with crizotinib for the company's preferred analysis, and Figure 5 shows the ERG preferred analysis. The company's preferred analysis shows [redacted] which are unreliable given the very small number of patients left at risk (Figure 4). The ERG's analysis using the updated data for PROFILE 1001 shows a more meaningful curve for crizotinib [redacted]

Figure 4. KM Plot of OS – company preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from CS, Figure 6)

Abbreviations: CS, company's submission; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

Figure 5. KM Plot of OS – ERG preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from company response to clarification, Figure 1)

Abbreviations: CS, company's submission; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; OS, overall survival.

Table 10. Overall survival – MAIC of entrectinib versus crizotinib (PROFILE 1001)

	Company preferred analysis			ERG preferred analysis		
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (data from TA529)**	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (Shaw 2019)**
Sample size	[redacted]	[redacted]	53	[redacted]	[redacted]	53
Number of events (%)	[redacted]	[redacted]	16 (30.1%)	[redacted]	[redacted]	27 (50.9%)
Median OS, months (95% CI)	[redacted]	[redacted]	NR (NR, NR)	[redacted]	[redacted]	51.5 (30.37, NE)
HR vs crizotinib (95% CI)	[redacted]	[redacted]	-	[redacted]	[redacted]	-

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; NE, not estimable; NR, not reached; OS, overall survival.
Data from CS Table 19 and the company's additional response to clarification.

The company rightly highlight that heavy censoring introduces uncertainty in the results, but a [redacted] proportion of patients contributed events in both arms of the ERG's analysis. Censoring was required for 69.8% of the crizotinib group in the company's analysis and 49.1% of patients in the ERG's preferred analysis using the updated PROFILE 1001 data. In the entrectinib group, the ERG's preference to remove the minimum follow-up restriction, which the company expected would lead to more censoring, [redacted] the proportion of patients with events compared with the company's analysis ([redacted] versus [redacted]).

The ERG highlights that information about disease stage and brain metastases at baseline were not available for PROFILE 1001 and are known to impact survival, so the comparison of entrectinib versus crizotinib could be confounded by these and other unknown and unmeasured differences between the populations. The ERG's clinical experts do not expect differences in the prior therapies received to introduce important bias in the comparison.

The ERG's clinical experts outlined that treatment with TKIs may continue beyond the first signs of radiological progression in clinical practice if the patient is well and continuing to derive benefit from treatment, and this has been found to improve OS in patients receiving crizotinib for advanced ALK+ NSCLC.[47] The ERG also notes that the extent of treatment beyond progression, and the type of subsequent therapies, are both unknown for PROFILE 1001 and so it is not possible to assess whether OS is biased, and in which direction.

Finally, median OS for crizotinib at the later follow-up of PROFILE 1001 was 51.4 months (95% CI: 30.37 to NE),[37] which the ERG's clinical experts outline is much longer than has been achieved in clinical practice. The company's alternative MAIC using real-world data for crizotinib in ROS1+ NSCLC from the US Flatiron registry gave a median OS for crizotinib of 18.5 months (15.1 to 19.9 months; CS Appendix D.5), but the median for entrectinib and the HR between treatments was [redacted].

The ERG does not consider the Flatiron comparison informative because it is likely to be biased in favour of entrectinib for which there are no equivalent real-world data.

4.4.3.2 Progression-free survival

The company's analysis suggests that entrectinib is [redacted] to crizotinib in terms of PFS ([redacted]), whereas the ERG's preferred analysis suggests there may be a [redacted] of crizotinib may be [redacted]). [redacted] The inverse of the HR is applied to the extrapolated entrectinib PFS curve to estimate the PFS curve for crizotinib (see Section 5.3.5). Figure 6 is a KM plot showing PFS for entrectinib before and after reweighting compared with crizotinib for the company's preferred analysis, and Figure 7 shows the ERG's preferred analysis. Figure 7 shows how the entrectinib curve is brought closer to crizotinib after reweighting but remains [redacted] the crizotinib curve for the duration of follow-up.

Figure 6. KM Plot of PFS (BICR) – company preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from CS, Figure 7)

Abbreviations: BICR, blinded independent central review; CS, company's submission; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.

Figure 7. KM Plot of PFS (BICR) – ERG preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from company response to clarification, Figure 2)

Abbreviations: BICR, blinded independent central review; CS, company's submission; ERG, evidence review group; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.

Table 11. PFS (BICR) – MAIC of entrectinib versus crizotinib (PROFILE 1001)

	Company preferred analysis			**ERG preferred analysis**		
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (data from TA529)**	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (Shaw 2019)**
Sample size	[redacted]	[redacted]	53	[redacted]	[redacted]	53
Number of events	[redacted]	[redacted]	26	[redacted]	[redacted]	36
Median PFS, months (95% CI)	[redacted]	[redacted]	19.151 (14.708, NR)	[redacted]	[redacted]	19.33 (15.27, 40.37)
HR vs crizotinib (95% CI	[redacted]	[redacted]	NA	[redacted]	[redacted]	-

Abbreviations: BICR, blinded independent central review; CI, confidence interval; ERG, evidence review group; HR, hazard ratio; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.
Data from CS Table 20 and the company's additional response to clarification.

As for OS, the comparison of entrectinib versus crizotinib could be confounded by population differences in disease stage and the proportion of patients with CNS metastases at baseline, which are known to be prognostic of outcome and were unknown for PROFILE 1001. The ERG's clinical experts do not expect differences in the prior therapies received to introduce important bias in the comparison.

The company stated that it was unclear whether PFS reported in PROFILE 1001 was assessed by investigators (PFS INV) or BICR, and so conducted a secondary comparison using PFS INV data from the entrectinib studies. Full data were not provided for the ERG's preferred analysis, but the HR shown on Figure 9 is [redacted] favourable to crizotinib than the BICR analysis ([redacted]), which is also true for the company's efficacy set ([redacted]). The ERG considers the BICR measurement more robust and is unsure why the investigator assessment [redacted]. Figure 8 and Figure 9 show the KM plots for the company and ERG analysis of PFS INV, which both show [redacted] between treatments after entrectinib is reweighted, but the entrectinib curves lie [redacted] the crizotinib curve for the duration of follow-up.

Figure 8. KM Plot of PFS (INV) – company preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from CS, Figure 8)

Abbreviations: CS, company's submission; ERG, evidence review group; INV, investigator-assessed; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.

Figure 9. KM Plot of PFS (INV) – ERG preferred MAIC of entrectinib versus crizotinib (PROFILE 1001; reproduced from company response to clarification, Figure 3)

Abbreviations: CS, company's submission; ERG, evidence review group; HR, hazard ratio; INV, investigator-assessed; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival.

Table 12. Investigator-assessed PFS – MAIC of entrectinib versus crizotinib (PROFILE 1001)

	Company preferred analysis			**ERG preferred analysis**		
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (data from TA529)**	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (Shaw 2019)**
Sample size	[redacted]	[redacted]	53	NR	NR	NR
Number of events	[redacted]	[redacted]	26	NR	NR	NR
Median PFS, months (95% CI)	[redacted]	[redacted]	19.151 (14.708, NR)	NR	NR	NR
HR vs crizotinib (95% CI	[redacted]	[redacted]	-	NR	NR	[redacted]

Abbreviations: CI, confidence interval; ERG, evidence review group; HR, hazard ratio; INV, investigator assessed; MAIC, matching adjusted indirect comparison; PFS, progression free survival.
Data from CS Table 21 and Figure 3 in the company's response to clarification.

The company accept that PFS is shorter in clinical practice than in PROFILE 1001 (CS, pg. 120) and conducted an alternative MAIC using real-world data for crizotinib in ROS1+ NSCLC from the US Flatiron registry and the BICR data for their preferred entrectinib efficacy set. The alternative Flatiron MAIC shows median PFS of [redacted] months for entrectinib ([redacted]) and 8.8 months for crizotinib (95% CI: 8.2 to 9.9 months), with an HR for entrectinib vs crizotinib of [redacted] (CS Appendix D.5, Table 33). As for OS, the ERG does not consider the Flatiron

comparison informative because it is likely to be biased in favour of entrectinib for which there are no equivalent real-world data.

4.4.3.3 Overall response rate

The company's analysis shows a [redacted] of entrectinib compared with crizotinib for ORR ([redacted]), which is not apparent in the ERG's preferred analysis ([redacted]; see Table 13). The ORR in each analysis shows that the proportion of patients (reweighted) responding in the ERG's preferred efficacy set for entrectinib is [redacted] than the company's primary efficacy set ([redacted]), and the proportion of patients responding to crizotinib in PROFILE 1001 was higher at the later follow-up than the data cut used by the company (71.7% vs 62.3%).

Table 13. Objective response rate – MAIC of entrectinib versus crizotinib (PROFILE 1001)

	Company preferred analysis			ERG preferred analysis		
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (data from TA529)**	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Crizotinib (Shaw 2019)**
Sample size	[redacted]	[redacted]	53	[redacted]	[redacted]	53
N (%) with ORR	[redacted]	[redacted]	33 (62.26)	[redacted]	[redacted]	38 (71.7)
OR vs crizotinib (95% CI)	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; ERG, evidence review group; MAIC, matching adjusted indirect comparison; N, number of patients; OR, odds ratio; ORR, objective response rate.
Data from CS Table 22 and the company's response to clarification Table 19

4.4.3.4 Adverse events

Discontinuation due to AEs was an outcome for the MAICs, but comparative data for specific AEs used in the economic model are based on unadjusted single-arm data for the company's preferred efficacy set (n = 53) and PROFILE 1001 (n = 53). A naïve comparison of the entrectinib safety set (n = [redacted]) and PROFILE 1001 was provided in CS Appendix F and is not reproduced here. The ERG agrees with the company that the naïve comparison is unreliable because it does not account for differences in the definitions used between trials, and both only report specific events that occurred in at least 10% of patients (or 2% for Grade 3 and above). Adverse event rates used in the economic model are discussed in Section 5.3.6.

The company's MAIC of discontinuation due to AEs suggest that a similar proportion of patients taking entrectinib and those taking crizotinib discontinue treatment due to AEs ([redacted] vs 7.54%). The ERG agrees with the company that, while the OR is in [redacted], the proportions of patients after reweighting are [redacted] and the confidence interval around the OR is wide ([redacted]). Analysis for this outcome was based on the ROS1+ safety population ([redacted]) from the entrectinib integrated analyses, so there was no difference between the ERG and company preferred analyses.

Table 14. Discontinuation due to AEs – MAIC of entrectinib versus crizotinib (PROFILE 1001)

Intervention	Entrectinib unadjusted	Entrectinib reweighted	Crizotinib (data from TA529)
Sample size	[redacted]	[redacted]	53
N (%) discontinued due to AEs	[redacted]	[redacted]	4 (7.54)
OR vs crizotinib (95% CI)	[redacted]	[redacted]	NR

Abbreviations: AEs, adverse events; CI, confidence interval; MAIC, matching adjusted indirect comparison; N, number of patients; OR, odds ratio; Data from CS Table 23.

4.4.4 Results for entrectinib versus PEM+PLAT

4.4.4.1 Overall survival

The company's analysis suggests a [redacted] OS benefit of entrectinib versus PEM+PLAT ([redacted]) than the ERG's preferred analysis ([redacted])

As described previously, results of the MAIC with ASCEND-4 were not used to estimate OS for PEM+PLAT in the company's base case; but were explored in a scenario analysis (see Section 5.3.5). OS estimates from the approach of applying HRs from PROFILE 1014 to results of the entrectinib versus crizotinib MAIC, which was the company's preferred method of deriving estimates for PEM+PLAT in the economic model, are discussed with the review of cost-effectiveness (Section5.3.5).

Figure 10 is a KM plot showing OS for entrectinib before and after reweighting compared with PEM+PLAT for the company's preferred analysis, and Figure 11 shows the ERG's preferred analysis. The company's analysis shows a [redacted], whereas the ERG's preferred analysis [redacted]

Figure 10. KM plot of OS – company preferred MAIC of entrectinib versus PEM+PLAT with pemetrexed maintenance (ASCEND-4; reproduced from CS, Figure 9)

Abbreviations: CS, company's submission; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; OS, overall survival; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.

Figure 11. KM plot of OS – ERG preferred MAIC of entrectinib versus PEM+PLAT with pemetrexed maintenance (ASCEND-4; reproduced from the company's response to clarification, Figure 5)

Abbreviations: CS, company's submission; ERG, evidence review group; HR, hazard ratio; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; OS, overall survival; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.

Table 15. Overall survival – MAIC of entrectinib versus PEM+PLAT (ASCEND-4)

	Company preferred analysis		ERG preferred analysis		PEM+PLAT (ASCEND-4)
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Entrectinib unadjusted**	**Entrectinib reweighted**	
Sample size	[redacted]	[redacted]	[redacted]	[redacted]	187
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	59*
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	26.26 (22.84, NE)
HR vs PEM+PLAT (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; ERG, evidence review group; HR, hazard ratio; MAIC, matching adjusted indirect comparison; OS, overall survival; PEM+PLAT, pemetrexed plus platinum therapy with pemetrexed maintenance.
Data from CS Table 24 and the company's additional response to clarification. *Number of events reported as 59 in the company's additional response to clarification and 84 in CS Table 24 but median OS was the same in both tables.

Treatment beyond the first signs of radiological progression can bias OS but is unlikely to be an issue here because PFS and TTD for entrectinib are similar and treatment with PEM+PLAT is a fixed number of cycles. However, imbalances in subsequent treatments that would not be given in the UK may introduce bias. Most notably, patients receiving PEM+PLAT in ASCEND-4 were previously untreated and, at the time of analysis, 42.7% had crossed over to receive ceritinib after progression (and 105/187 [51.6%] had received any ALK inhibitor),[70] whereas patients would receive targeted treatments prior to PEM+PLAT in UK clinical practice (see Section 2.2). As a result, the survival benefit of entrectinib versus PEM+PLAT as a second-line therapy is likely to be underestimated. The ERG acknowledges that all patients were previously untreated in ASCEND-4, whereas patients in the entrectinib studies were further down the treatment pathway but does not consider this an important bias because the populations were matched for baseline disease stage and performance status.

4.4.4.2 Progression-free survival

The company's analysis ([redacted]) and the ERG's analysis ([redacted]) both show [redacted] for PFS with entrectinib than PEM+PLAT. Figure 12 is a KM plot showing PFS for entrectinib before and after reweighting compared with PEM+PLAT for the company's preferred analysis, and Figure 13 shows the ERG's preferred analysis. Both show that reweighting [redacted] the difference between treatments. PFS estimates from the approach of applying HRs from PROFILE 1014 to results of the entrectinib versus crizotinib MAIC, which was the company's preferred method of deriving estimates for PEM+PLAT in the economic model, are discussed with the review of cost-effectiveness (Section 5.3.5).

Figure 12. KM plot of PFS (BICR) – company preferred MAIC of entrectinib versus PEM+PLAT with pemetrexed maintenance (ASCEND-4; reproduced from CS, Figure 10)

Abbreviations: BICR, blinded independent central review; CS, company's submission; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.

Figure 13. KM plot of PFS by BICR – ERG preferred MAIC of entrectinib versus PEM+PLAT with pemetrexed maintenance (ASCEND-4; reproduced from company response to clarification, Figure 6)

Abbreviations: BICR, blinded independent central review; CS, company's submission; ERG, evidence review group; HR, hazard ratio; KM, Kaplan–Meier; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.

Table 16. PFS (BICR) – MAIC of entrectinib versus PEM+PLAT (ASCEND-4)

	Company preferred analysis		ERG preferred analysis		PEM+PLAT (ASCEND-4)
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Entrectinib unadjusted**	**Entrectinib reweighted**	
Sample size	[redacted]	[redacted]	[redacted]	[redacted]	187
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	117
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	7.99 (5.7, 11.13)
HR vs PEM+PLAT (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: BICR, blinded independent central review; CI, confidence interval; ERG, evidence review group; HR, hazard ratio; MAIC, matching adjusted indirect comparison; PFS, progression-free survival; PEM+PLAT, pemetrexed plus platinum therapy with pemetrexed maintenance.
Data from CS Table 25 and the company's additional response to clarification.

As for OS, the ERG acknowledges that all patients were previously untreated in ASCEND-4, whereas patients in the entrectinib studies were further down the treatment pathway but does not consider this an important bias because the populations were matched for baseline disease stage and performance status. Moreover, the ERG has the same reservations about the reliability of PFS estimates that were expressed for OS regarding the appropriateness of using evidence for PEM+PLAT from an ALK+ NSCLC population.

4.4.4.3 Overall response rate

The company's analysis shows a [redacted] of entrectinib compared with PEM+PLAT for ORR ([redacted]) as does the ERG's preferred analysis ([redacted]), although to a [redacted] extent (see Table 17). The ORR in each analysis shows that the proportion of patients (reweighted) responding in the ERG's preferred efficacy set for entrectinib is somewhat [redacted] than the company's primary efficacy set ([redacted]), but both are [redacted] than the 26.7% ORR for PEM+PLAT.

Table 17. Objective response rate – MAIC of entrectinib versus PEM+PLAT (ASCEND-4)

	Company preferred analysis		ERG preferred analysis		PEM+PLAT (ASCEND-4)
Intervention	**Entrectinib unadjusted**	**Entrectinib reweighted**	**Entrectinib unadjusted**	**Entrectinib reweighted**	
Sample size	[redacted]	[redacted]	[redacted]	[redacted]	187
N (%) with ORR	[redacted]	[redacted]	[redacted]	[redacted]	50 (26.7)
OR vs PEM+PLAT (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: CI, confidence interval; ERG, evidence review group; HR, hazard ratio; MAIC, matching adjusted indirect comparison; ORR, objective response rate; PEM+PLAT, pemetrexed plus platinum therapy with pemetrexed maintenance.
Data from CS Table 26 and the company's response to clarification Table 21.

4.4.4.4 Adverse events

Discontinuation due to AEs was an outcome for the MAICs, but comparative data for specific AEs used in the economic model are based on unadjusted single-arm data for the company's preferred efficacy

set (n = 53) and the PEM+PLAT arm of PROFILE 1014 (n = 171). Adverse event rates used in the economic model are discussed in Section 5.3.6.

The company's MAIC of discontinuation due to AEs suggest that a [redacted] proportion of patients taking entrectinib and PEM+PLAT discontinue treatment due to AEs ([redacted] vs 8.56%). The proportions of patients after reweighting are similar and the confidence interval around the OR is wide ([redacted]). Analysis for this outcome was based on the ROS1-positive safety population (n=134) from the entrectinib integrated analyses, so there was no difference between the ERG and company preferred analyses.

Table 18. Discontinuation due to AEs – MAIC of entrectinib versus PEM+PLAT (ASCEND-4)

Intervention	Entrectinib unadjusted	Entrectinib reweighted	PEM+PLAT
Sample size	[redacted]	[redacted]	187
N (%) discontinued due to AEs	[redacted]	[redacted]	16 (8.56)
OR vs PEM+PLAT (95% CI)	[redacted]	[redacted]	-

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients; OR, odds ratio; PEM+PLAT, pemetrexed plus platinum therapy with pemetrexed maintenance.
Data from CS Table 27 and the company's additional response to clarification.

4.5 Summary and conclusions of the clinical effectiveness section

Background and treatment pathway

- ROS1+ NSCLC is very rare (1-2% of NSCLC) and tends to affect younger patients with light or no smoking history. The ROS1 oncogenic driver can be targeted with tyrosine kinase inhibitors and is now included in the standard genomic tissue testing conducted when patients are diagnosed with non-squamous NSCLC;

- Entrectinib is an oral, CNS-active, potent inhibitor of the tyrosine kinases encoded by the ROS1, NTRK1, NTRK2, NTRK3 and ALK genes. The anticipated marketing authorisation for entrectinib, expected in [redacted], is [redacted] following confirmation of ROS1+ status;

- The company propose that entrectinib will be used at first- or second-line for patients with ROS1+ NSCLC. The ERG's clinical experts agreed that crizotinib (only available through the CDF) and pemetrexed plus platinum therapy (PEM+PLAT) are the relevant comparators for entrectinib, and all other comparators listed in the NICE final scope would be used later in the treatment pathway.

Clinical effectiveness evidence for entrectinib

- Clinical effectiveness evidence supporting the use of entrectinib for patients with ROS1+ NSCLC is available from three ongoing, mixed population, single-arm, open label studies – ALKA (n = 58; Italy), STARTRK-1 (n = 76; USA, South Korea and Spain) and STARTRK-2 (n = 207; Australia, Europe, Asia and the USA). All three studies are recruiting mixed populations of patients with locally advanced or metastatic solid tumours testing positive for ROS1, ALK, or NTRK1/2/3 genetic alterations;

- The company's primary efficacy analyses are based on an integrated analysis of patients from all three studies with ROS1-inhibitor naïve ROS1+ NSCLC, measurable disease at baseline, and at least 12 months' follow-up (n = 53). The primary outcome was ORR by BICR in line with STARTRK-2, and secondary outcomes included OS, PFS (BICR), HRQoL, intracranial response and PFS, and safety;

- The ERG's considers an efficacy set with no follow-up restriction including patients with ROS1-inhibitor naïve ROS1+ NSCLC who received entrectinib in line with its intended marketing authorisation (which could only be confirmed for STARTRK-2), more appropriate for decision making. [redacted] patients were excluded from the company's analyses for having follow-up < 12 months;

- The ERG and company preferred analyses of entrectinib are based on single-arm data and are therefore considered low quality evidence. The 12-month minimum follow-up restriction to define the company's primary efficacy set for the integrated analysis may introduce selection bias. The ERG notes that the power calculation for the company's integrated analysis was based on ORR and so the company's primary efficacy set for the integrated analysis was not necessarily powered for OS or PFS;

- The company and the ERG preferred efficacy sets for the entrectinib analyses are considered representative of patients with ROS1+ NSCLC in the UK (mean age ~53 years, ~60% female, ~90% ECOG PS 0 or 1 and ~40% with a history of smoking). The proportion of Asian patients is higher in the ERG preferred (46.2%) and company efficacy sets (35.8%) than in the UK, but race is not known to affect disease course or response to treatment in ROS1+ NSCLC;

- Baseline characteristics are mostly comparable between the company and ERG preferred efficacy sets but the ERG's preferred efficacy set more often had adenocarcinoma (97.4 vs 76.1%) and a higher proportion had Stage IV disease (73.1 vs 61.4%), but nearly all patients had metastatic disease at study baseline (>94%) and a similar proportion had brain metastases (~44%), which have an important impact on prognosis and quality of life. Approximately two thirds of the company and the ERG efficacy sets for the analyses of entrectinib had received at

least one prior systemic therapy before entrectinib (~70%), some of which are not available in the UK, meaning the effectiveness of entrectinib for untreated ROS1+ NSCLC may be underestimated;

- The primary outcome of ORR (BICR) in the company's primary integrated analysis of ALKA, STARTRK-1 and STARTRK-2 (CCOD 31 May 2018) was [redacted] ([redacted] complete and [redacted] partial response) and median DoR was [redacted] ([redacted] months, 95% CI: [redacted]). Median OS was not estimable in the company's primary analysis (median follow-up 15.5 months; [redacted] deaths [[redacted]]) and median PFS was [redacted] months (95% CI: [redacted] months);

- In the ERG's preferred analysis including 78 patients from STARTRK-2 who all received the recommended 600 mg dose of entrectinib, ORR by BICR was slightly [redacted] at [redacted] and median DoR was [redacted] ([redacted] months; 95% CI [redacted]). There were more deaths in the ERG's preferred analysis and median OS was [redacted] months (mean follow-up 13.3 months; [redacted] deaths [[redacted]]), but the data are still immature and so the median is unreliable, and median PFS was [redacted] than the company's analysis at [redacted] months (95% CI [redacted]);

- The ERG accepts that removing the minimum follow-up restriction means that DoR is likely to be more stable in the company's preferred analysis but considers the ERG's analysis preferable for the efficacy outcomes reflected in the economic model (OS and PFS) because they include a high number of patients and events and all scans in STARTRK-2 were assessed prospectively;

- Intracranial outcomes were not listed in the NICE final scope, but results presented in the submission provide some support for the proposed activity of entrectinib for CNS disease. The ERG's clinical experts expressed the need for CNS-active treatments because brain metastases are common with ROS1+ NSCLC and have a profound impact on prognosis and quality of life. Intracranial outcomes were not analysed in the MAICs conducted to compare entrectinib with crizotinib or PEM+PLAT and are not reflected in the economic model;

- HRQoL data for entrectinib were collected in STARTRK-2 and suggest patients in the company's and the ERG's preferred efficacy sets had moderate-to-high functioning and moderate lung cancer symptom burden at baseline. While the company highlights particular time points where some scores peaked (e.g. improvement in severe cough after the first dose) the ERG considers there to be some indication of deterioration in global health status, functioning and symptom domains of the EORTC QLQ-C30 between baseline and the end of treatment. Symptom burden scores were relatively stable on the EORTC LC-13, with only dyspnoea showing a clear sign of worsening, but variation between means and medians in each efficacy set and large SDs and ranges suggest a great deal of variation within the population;

- Safety analysis were conducted on a wider population than the efficacy sets, including all ROS1+ NSCLC patients who received at least one dose of entrectinib in ALKA, STARTRK-1 and STARTRK-2 irrespective of prior ROS1-inihibitor therapy, measurable disease at baseline, dose or follow-up ([redacted]). [redacted] of patients experienced at least one AE and [redacted] of patients were deemed to have a treatment-related AE. Treatment-related Grade 3 or higher AEs occurred in [redacted] of the ROS1+ patients and treatment-related SAEs in [redacted]% of patients. The most frequently reported treatment related AEs in the ROS1+ population were dysgeusia ([redacted]%), dizziness ([redacted]%), constipation ([redacted]%), diarrhoea ([redacted]), weight increase ([redacted]), and fatigue ([redacted]%). AEs led to dose interruption in [redacted] of ROS1+ patients and dose reduction in [redacted] of ROS1+ patients.

Subgroup analyses

- A subgroup analysis in line with the NICE final scope suggests that PFS is likely to be [redacted] and response rates [redacted] for patients with CNS disease than those without CNS disease at baseline, but formal significance tests were not performed. Differences in PFS and DOR for patients with and without CNS disease at baseline were far more pronounced in the company's preferred analysis (PFS [redacted] versus [redacted] months; DoR [redacted] versus [redacted] months) than ERG's preferred analysis. The ERG highlights that all subgroup analyses are based on small numbers of events and, for OS, immature survival follow-up.;

- A *post hoc* subgroup analysis requested by the ERG does not suggest prior TKI use is an important effect modifier for OS, PFS and ORR, but the ERG notes that patients who had received a prior ROS1-targeted TKI and were excluded from the company's and the ERG's preferred efficacy sets, which the clinical experts considered appropriate. Further prespecified subgroup analyses for the primary outcome of ORR showed rates of [redacted] to [redacted] across subgroups for entrectinib dose (below 600 mg, 600 mg and above 600 mg), ECOG performance status (0, 1, 2, ≥3), and a range of subgroups to explore type and number of prior anticancer therapies (systemic, chemotherapy, targeted, hormonal, radiation, surgery and brain radiation). The ERG does not consider there to be a sufficient number of patients to draw any meaningful conclusions about subgroup differences.

Indirect treatment comparisons with crizotinib and PEM+PLAT

- The entrectinib studies provide no comparative data and so SLRs were carried out by the company to identify studies to support MAICs between entrectinib and the relevant comparators, crizotinib and PEM+PLAT. Outcomes addressed in the MAICs were OS, PFS, ORR and discontinuation due to AEs, but only OS and PFS are reflected in the economic model.

The company took an 'all lines' approach for the MAICs because around [redacted] of patients with ROS1+ NSCLC in the entrectinib studies had received prior systemic therapy and the population was too small to support separate analyses by line of treatment;

- PROFILE 1001 – a multicentre Phase I single-arm study of crizotinib for ROS1+ NSCLC (n = 53) – was chosen to support an MAIC of entrectinib versus crizotinib. The ERG notes the following with regard to the MAIC based on PROFILE 1001:
    - While it does not provide comparative data, the ERG's clinical experts agree that PROFILE 1001 is the most robust evidence for crizotinib in a ROS1+ NSCLC population.
    - Like the entrectinib studies, PROFILE 1001 included a mixed population of treatment-naïve and pre-treated patients and the primary outcome was ORR by IRR.
    - The company and ERG preferred efficacy sets for entrectinib were reweighted to match PROFILE 1001 for sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, prior treatments (treatment naïve vs prior treatment), and age. Data were not available to match for disease stage and presence of CNS metastases which are known to impact survival, so results could be confounded by these and other unknown differences between the populations.
- ASCEND-4 – a large, multicentre, Phase III RCT of ceritinib versus PEM+PLAT (with pemetrexed maintenance therapy) for untreated ALK+ NSCLC (n = 187 in the PEM+PLAT group) – was chosen to inform an MAIC of entrectinib versus PEM+PLAT because there were no studies in an ROS1+ NSCLC. The ERG notes the following with regard to the MAIC based on ASCEND-4:
    - ASCEND-4 is a well conducted RCT and, while other ALK+ NSCLC studies were identified that include a PEM+PLAT arm, ASCEND-4 is the only study to give pemetrexed maintenance therapy as is done in UK clinical practice.
    - The ERG considers there to be no consensus about the appropriateness of using evidence from ALK+ NSCLC as a proxy for ROS1+ NSCLC, and there is no way to quantify or adjust for differences in treatment effect that are attributable to the underlying gene fusion. Patients with ALK+ and ROS1+ NSCLC share demographic similarities (younger age than wider NSCLC population, higher proportion of non-smokers, primarily adenocarcinoma histology), treatments are comparable, and the kinases are homologous, but the appraisal committee for TA529 considered the use of

evidence for ALK+ NSCLC "very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals."[12]

- At the time of analysis, 42.7% of patients who received PEM+PLAT had crossed over to receive ceritinib (80/187), and 51.6% had received any subsequent ALK inhibitor (105/187),[70] so the survival benefit of PEM+PLAT is likely overestimated.

- The study recruited only patients with untreated disease which could not be adjusted for because most patients in the entrectinib studies had received prior systemic therapies. However, the company's and the ERG's preferred efficacy sets for entrectinib were reweighted to match ASCEND-4 for sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, age, and disease stage (stage IIIB vs stage IV non-CNS metastasis vs stage IV CNS metastasis).

- The company use an alternative method to derive estimates of OS and PFS for PEM+PLAT in the economic model using PROFILE 1014 and use the ASCEND-4 MAIC as a scenario analysis. The ERG considers there to be important limitations of both methods used to derive estimates for PEM+PLAT but considers the estimates of ASCEND-4 more clinically plausible. PROFILE 1014 is a multicentre, open-label RCT that compared crizotinib to PEM+PLAT for patients with untreated ALK+ NSCLC. The company apply HRs to the results from the entrectinib versus crizotinib MAIC to derive OS and PFS estimates for PEM+PLAT. The ERG accepts that this method retains the benefits of a randomised comparison and only assumes that the *relative* effect of crizotinib versus PEM+PLAT is similar for ALK+ and ROS1+ NSCLC but PEM+PLAT was not given with pemetrexed maintenance therapy and the proportional hazards assumption does not hold for PFS. Furthermore, the company use crossover-adjusted OS using a method which was deemed flawed by the appraisal committee for TA529. Unadjusted results were considered preferable for TA529 because only 19% of patients had crossed over, but 84% had done so at the latest follow-up so this is no longer be reasonable.

- The company's MAIC based on PROFILE 1001 suggests that entrectinib has a trend towards benefit over crizotinib for OS ([redacted]) and better ORR ([redacted]), but the treatments may offer similar PFS ([redacted]). The ERG's preferred MAIC using PROFILE 1001 suggests a [redacted] OS benefit of entrectinib compared with crizotinib ([redacted]) than the MAIC using the company's preferences. The ERG's results also show different effects to the company's for ORR and PFS, with the ERG's preferred MAIC suggesting [redacted] in ORR between the treatments ([redacted]) and a trend towards [redacted] of crizotinib over entrectinib for PFS [redacted]. A sensitivity analysis using PFS INV

data from the entrectinib studies was [redacted] favourable to crizotinib than the BICR analysis using the ERG's preferences ([redacted]), and the company's ([redacted]);

- The company's MAIC based on ASCEND-4 suggests that entrectinib also has [redacted] benefits over PEM+PLAT for OS ([redacted]), PFS ([redacted]) and ORR ([redacted]). Results from the ERG's preferred MAIC all lie in favour of entrectinib, but effects are somewhat [redacted] than the company's preferred MAIC for OS ([redacted]), PFS [redacted] and ORR ([redacted]). The ORR in each analysis shows that the proportion of patients (reweighted) responding in the ERG's preferred efficacy set for entrectinib is somewhat [redacted] than the company's primary efficacy set ([redacted]), but both are [redacted] than the 26.7% ORR for PEM+PLAT;

- After reweighting, both MAICs suggest that a similar proportion of patients discontinue entrectinib due to AEs as crizotinib ([redacted] vs 7.54%) and PEM+PLAT ([redacted] vs 8.56%), based on the wider ROS1+ NSCLC safety population for entrectinib. AEs in the economic model are based on naïve comparisons.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL based economic model. As a result of the clarification stage, the company submitted an updated economic model, which constitutes the focus of this review.

In the company's base case analysis, treatment effectiveness for the entrectinib arm of the model was estimated with integrated data from ALKA, STARTRK-1 and STARTRK-2 [clinical cut-off date (CCOD 31 May)]. During the clarification stage, the ERG requested that the company changed their entrectinib analysis set to reflect the ERG's preferred efficacy set. The latter consisted on using only the STARTRK-2 study, with a CCOD 30 October, and including all patients who received 600mg entrectinib, irrespective of response or follow-up duration. The ERG asked the company to use these data to fit entrectinib OS, PFS and TTD curves in the economic model, and to re-run both MAICs comparing entrectinib with crizotinib and pemetrexed plus platinum chemotherapy (PEM+PLAT). Similarly, the ERG requested that the company used the more mature PROFILE 1001 data from Shaw 2019 to re-run the matching adjusted indirect comparison (MAIC) comparing entrectinib with crizotinib.[46]

The company has provided the ERG with all the requested analyses (except using the most up to date CCOD data available from STARTRK-2), although did not change their base case, which relied on the integrated entrectinib data, and the more immature PROFILE 1001 data. Given the ERG's disagreement with the company's choice of analysis set, the ERG focusses its description and critique of the company's approach using the ERG's preferred efficacy set throughout Section 5 of this report. The details of the rationale for the ERG's preference is discussed at length in Section 4 of the ERG report. Results (and description) of the company's base case analysis using the company's preferred efficacy set are reported where deemed relevant (and summarised in Section 5.4).

5.2 ERG comment on company's review of cost-effectiveness evidence

The company conducted three separate systematic reviews (SLRs) to search for economic evaluations, health-related quality-of-life (HRQoL) studies, and studies informing healthcare resource use and costs, each relating to treatment for people with ROS1 positive non-small cell lung cancer (ROS1+ NSCLC). Each review is described in turn in Sections 5.2.1 to 5.2.3.

5.2.1 Economic evaluations

The company searched the following databases for economic evaluations of pharmacological interventions for the treatment of ROS1+ NSCLC on 27 March 2019: Embase, MEDLINE, The Cochrane Library (*The Health Technology Assessment [HTA] database and the National Health Service Economic Evaluation Database [NHS EED]*), EconLit®.

In addition to these searches, the company hand-searched: reference lists of the included studies; conference proceedings (*American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO], International Society for Pharmacoeconomics and Outcomes Research [ISPOR], Health Technology Assessment International [HTAi]*); and, HTA body websites (*National Institute for Health and Care Excellence [NICE], Scottish Medicines Consortium [SMC], Pharmaceutical Benefits Advisory Committee [PBAC], Canadian Agency for Drugs and Technologies in Health [CADTH] - including the pan-Canadian Oncology Drug Review [pCODR]*).

The company also searched: The Cost Effectiveness Analysis (CEA) Registry; EconPapers within Research Papers in Economics (RePEc); University of York Centre for Reviews and Dissemination (CRD), HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA); National Institute for Health Research (NIHR) HTA database; and, Google Scholar. More details on the company's search strategy can be found in Appendix G of the CS, along with the terms included in the search and inclusion and exclusion criteria applied to identify relevant studies.

Combining search terms for the ROS1+ NSCLC population with economic search terms, the company found 87 studies from Embase, 20 from MEDLINE, and zero from both Cochrane Library and EconLit. From that total of 107 studies, 92 studies were put through a title and abstract review, after 15 duplicates were removed. Nine of the studies screened were considered potentially relevant but were all subsequently excluded after full-text review. Reasons for exclusion are given in Table 43 of Appendix G.6 of the CS.

Three HTA submissions (two originals and one re-submission) were identified through hand-searching and these were included. These were: the NICE appraisal of crizotinib for both untreated and previously treated patients with ROS1+ NSCLC (TA529); the original PBAC appraisal of second-line crizotinib for patients with locally advanced (stage IIIB) or metastatic (stage IV) ROS1+ NSCLC; and, a resubmission to PBAC for the aforementioned crizotinib appraisal.

5.2.2 HRQoL

The company performed the HRQoL search using the same databases as for the economic evaluation search, described in Section 5.2.1, but also added the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) as part of the Cochrane

Library. The company also searched the same HTA body websites as for the economic evaluation search.

The additional sources that were hand-searched for HRQoL evidence differed from those in the economic evaluation search as they were more focused on utility specific sources. The utility-specific ones were, namely, the EuroQoL website and the University of Sheffield ScHARRHUD utility database. The company also searched CRD, INAHTA, NIHR HTA databases and Google Scholar, as per the economic evaluation search. More details on the company's search strategy can be found in Appendix H of the CS, along with the terms included in the search and inclusion and exclusion criteria applied to identify relevant studies.

Combining search terms for the ROS1+ NSCLC population with search terms relating to quality of life and utilities resulted in 32 studies from Embase, two from MEDLINE and zero from the Cochrane Library. After removing two duplicates the remaining 32 studies went through a title and abstract screening and the company identified six potentially relevant studies that received a full text review. The company subsequently excluded all of these studies. Reasons for exclusion are given in Table 48 of Appendix H.6 of the CS. No additional studies were identified through hand-searching.

5.2.3 Resource use and costs

To identify relevant unit cost and resource use data, the company searched for evidence using Embase, MEDLINE, NHS EED, CRD HTA and EconLit®, as well as the websites of the HTA bodies in the UK; namely, NICE, SMC and AWMSG. The company also searched conference proceedings from the last 2 years (2017 and 2018) from ISPOR, ASCO and ESMO.

Combining search terms for the ROS1+ NSCLC population with search terms relating to costs and resources use resulted in 795 studies from Embase, 139 from MEDLINE, 33 from NHSEED, 82 from CRD HTA, and 6 from EconLit®. After 11 duplicates were removed, 1044 studies went through a title and abstract screening. Of these, 180 articles received a full-text review and all studies were excluded. Reasons for exclusion are given in Table 55 of Appendix I.6 of the CS. Two HTAs were also identified by the company through hand-searching, although details of these were not explicitly given.

5.2.3.1 ERG critique

The ERG considers the company's SLR to be generally sound and likely to have identified all of the key studies relating to ROS1+ NSCLC patients. However, given the lack of evidence and the requirement for additional studies in similar populations such as the ALK+ NSCLC population, the ERG considers that the company could have performed a broader SLR to incorporate a wider population. Despite this, the ERG considers it unlikely that any alternative sources exist to provide more robust and reliable data. Due to time constraints, the ERG was unable to replicate the SLR.

5.3 Overview and critique of company's economic evaluation based on the ERG's preferred efficacy set

5.3.1 NICE reference case checklist

Table 19 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.

Table 19. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Unclear. There was consensus amongst the clinical experts advising the ERG that if available, entrectinib would become the preferred first-line treatment for ROS1+ NSCLC patients. However, 73.1% of patients in the ERG's preferred efficacy set had received one or more systemic treatment before entrectinib. Therefore, the entrectinib population used in the economic analysis is a more accurate representation of patients treated in second-line rather than first-line. Nonetheless, advice from the ERG's clinical experts suggests that the impact of prior treatments on the assessment of entrectinib's effectiveness at first line is mitigated by the exclusion of patients who had received prior ROS1 inhibitors, which would have the biggest impact on the benefits of entrectinib. In the ERG's preferred efficacy set patients received prior TKI treatment, and prior immunotherapies. The ERG is unsure how this could affect the study outcomes in STARTRK-2 but notes that these treatments would not be available to patients with NSCLC in the NHS before crizotinib or entrectinib. Furthermore, in PROFILE 1001, 86% of the patients for whom data were available had received at least one prior therapy, including TKIs and immunotherapies. The proportion of patients who received each of the main systemic therapies is consistently [redacted] in the entrectinib studies than PROFILE 1001. The MAIC conducted by the company used the overall proportion of patients who had received prior therapy as a factor for matching, so the higher proportions of patients receiving key systemic treatments in PROFILE may bias against crizotinib if prior treatments reduce the effectiveness of crizotinib. Concerning PEM+PLAT, clinical experts advising the ERG explained that this is a relevant comparator to entrectinib for second-line treatment, after patients progressed on first-line crizotinib. The ERG notes that the same entrectinib data and population are used for the comparison of entrectinib against crizotinib and PEM+PLAT, when in fact these treatments are relevant comparators in different treatment lines.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes. The ERG agrees with the company's choice of crizotinib as the most relevant comparator for untreated disease (even though there is no evidence to substantiate this comparison in a first-line setting). The ERG also agrees with the inclusion of PEM+PLAT as a comparator in the economic analysis, however, notes that this is a relevant comparator to entrectinib for second-line treatment, after patients progressed on first-line crizotinib. Given that the anticipated use of entrectinib as a second-line treatment is reserved for cases where patients have already started crizotinib (so in theory patients on crizotinib before a potential recommendation of entrectinib), the relevance of PEM+PLAT as a comparator is reduced.

Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.3.2 Population

The population considered by the company for this STA comprises adults with locally advanced or metastatic ROS1+ NSCLC. The ERG's preferred efficacy set is limited to 78 patients from STARTRK-2, who constitute the population in the economic model.

There was consensus amongst the clinical experts advising the ERG that if available, entrectinib would become the preferred first-line treatment for ROS1+ NSCLC patients due to its CNS activity, compared to crizotinib. However, 57 patients (73.1%) in the ERG's preferred efficacy set had received one or more systemic treatment before entrectinib, leaving only 21 treatment-naïve patients (i.e. not having received prior systemic therapies). Therefore, the integrated entrectinib population used in the economic analysis is a more accurate representation of patients treated in second-line rather than first-line.

Nonetheless, advice from the ERG's clinical experts suggests that the impact of prior treatments on the assessment of entrectinib's effectiveness at first line is mitigated by the exclusion of patients who had received prior ROS1 inhibitors, which would have the biggest impact on the benefits of entrectinib. The experts added that prior chemotherapy treatments are not expected to have a major impact on entrectinib's effectiveness, but that the impact of other targeted therapies and immunotherapies is unknown. In the ERG's preferred efficacy set, [redacted] of patients had received prior TKI treatment, while [redacted] of patients received prior immunotherapies (with [redacted] receiving nivolumab and [redacted] receiving bevacizumab). The ERG is unsure how this could affect the study outcomes in STARTRK-2 but notes that these treatments would not be available to patients with NSCLC in the NHS before crizotinib or entrectinib.

In the ERG's preferred efficacy set, the relative treatment effectiveness of entrectinib vs crizotinib for untreated disease was obtained through an MAIC using the latest data cut-off from the PROFILE 1001 study.[46] In PROFILE 1001, 86% of the 50 patients for whom data were available had received at least one prior therapy, including TKIs (32%); bevacizumab (32%); gemcitabine (22%); and vinorelbine (6%). Therefore, the proportion of patients who received each of the main systemic therapies is consistently [redacted] in the entrectinib studies than PROFILE 1001. The MAIC conducted by the company used the overall proportion of patients who had received prior therapy as a factor for matching, so the higher proportions of patients receiving key systemic treatments in PROFILE may bias against crizotinib if prior treatments reduce the effectiveness of crizotinib.

In their base case model, the company estimated progression and survival with PEM+PLAT by applying a hazard ratio (HR) to the crizotinib progression and survival curves. Even though the HR was obtained from PROFILE 1014, the baseline crizotinib curve was based on the PROFILE 1001 population, therefore the PROFILE 1014 population is not directly used in the economic model. This issue is further discussed in Section 5.4.5.

5.3.3 Interventions and comparators

In the ERG's preferred efficacy set, the intervention considered in the economic model reflects that set out in the marketing authorisation given that only patients who received 600 mg entrectinib in STARTRK-2 were included in the analysis. The recommended dose for entrectinib is 600 mg, to be taken as three 200 mg oral capsules once daily, in repeated 30-day cycles. Entrectinib was administrated until disease progression or clinical deterioration in STARTRK-2. Time on treatment (ToT) data from STARTRK-2 for entrectinib were used in the base case to estimate the cost of entrectinib.

The NICE final scope did not restrict the population by prior treatment but listed comparators separately for untreated disease and after chemotherapy. The comparators included in the economic analysis depart, to some extent, from those specified in the NICE final scope.

Even though crizotinib was not listed in the NICE final scope, the ERG's clinical experts agree with the company that it is now the preferred treatment for untreated ROS1+ NSCLC. Concerning PEM+PLAT, clinical experts advising the ERG explained that this is a relevant comparator to entrectinib for second-line treatment, after patients progressed on first-line crizotinib. As the ERG's clinical experts expressed a preference for using entrectinib first line, rather than crizotinib, were entrectinib to receive a recommendation for use at first-line the relevance of PEM+PLAT as a comparator for second-line is reduced. The other treatments listed in the NICE final scope for treated and untreated disease (discussed in detail in Section 3.3) were considered irrelevant by the company, and by the ERG's clinical experts.

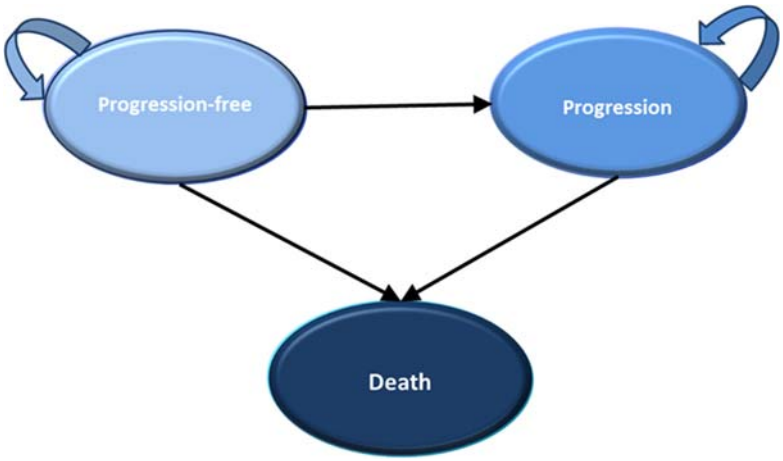
Therefore, the ERG agrees with the company's choice of crizotinib as the most relevant comparator for untreated disease, however, notes that there is no evidence to substantiate this comparison in a first-line setting, and that the analysis submitted by the company is mainly based on evidence for the second-line effectiveness of entrectinib and crizotinib. The ERG also agrees with the inclusion of PEM+PLAT as a comparator in the economic analysis, however, notes that the same entrectinib data are used for the comparison of entrectinib against crizotinib and PEM+PLAT, when in fact these treatments are relevant comparators in different treatment lines.

5.3.4 Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of entrectinib compared with crizotinib and PEM+PLAT in ROS1+ NSCLC patients. The cohort-based partitioned survival model (presented in Figure 14) includes three health states: progression-free survival (PFS), progressed disease (PD), and death. The cohort is allocated to the PFS state at the beginning of the economic analysis and is assumed to initiate treatment with entrectinib or with one of the comparators. Patients occupying the PFS state are at risk of disease progression or death and can also discontinue treatment before disease progression. Patients occupying the PD state are also at risk of death and receive further treatment lines in the model. After entering the PD state patients cannot enter remission.

The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

Figure 14. Model diagram



A life time horizon of 30 years was adopted in the model and time was discretised into 30-day cycles with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

5.3.4.1 ERG critique

The ERG is generally satisfied with the model structure. The partitioned survival approach employed by the company is appropriate. A life time horizon of 30 years seems plausible considering the baseline mean age of 53 years in the entrectinib integrated dataset and 54 years in PRFOFILE 1001.

Nonetheless, the company's base case economic analysis estimates that 30% of entrectinib patients are still alive at 10 years (while only 10% are alive at 10 years with crizotinib), with 7% of entrectinib patients alive at 20 years (when they would be 73). This suggests an overestimation of long-term survival in the model, especially for patients with metastatic disease. This issue is further discussed in Section 5.4.8 of the ERG report.

In the ERG's preferred efficacy set, 12% of entrectinib patients are still alive at 10 years (while only 5% are alive at 10 years with crizotinib), with 4% of entrectinib patients alive at 20 years (when they would be 73).

The ERG agrees with the use of the half-cycle correction given the monthly cycle length, however it noted that its implementation in the company's model meant that not 100% of patients were receiving the initial treatment dose in the first cycle of the economic model. The ERG asked the company to change this during the clarification stage, and results are provided in Section 6 of the ERG report.

5.3.5 Treatment effectiveness based on the ERG's preferred efficacy set

The CS reports that entrectinib is the first ROS1 inhibitor to show intracranial activity against ROS1-driven CNS metastases. The company adds that entrectinib offers a further targeted treatment option with improved clinical effectiveness and tolerability compared to non-targeted chemotherapy, and evidence of activity in the CNS, thus meeting an unmet medical need in current clinical practice.

Treatment effectiveness for the entrectinib arm of the model was estimated through a partitioned survival method, which used OS, PFS and ToT data from STARTRK-2 in the ERG's preferred efficacy set. The company fitted a variety of parametric models to the integrated Kaplan-Meier (KM) data using an exponential, Weibull, log-logistic, lognormal and generalised gamma models, and assessed the fit of each parametric model compared with the observed KM using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), in accordance with guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[48]

Overall survival and PFS for crizotinib were estimated from the MAIC using the ERG's preferred efficacy set for entrectinib and the latest data cut-off from the PROFILE 1001 study (described in detail in Section 4). The inverse of the estimated HRs from the MAIC were then applied to the fitted OS and PFS entrectinib curves. Time on treatment for crizotinib was assumed to the be the same as time until progression (i.e. PFS) as the company could not find any published ToT data for crizotinib.

In the base case analysis, OS and PFS for PEM+PLAT were estimated by applying the published OS and PFS HRs from PROFILE 1014 to the crizotinib arm of the model. As an alternative scenario, the company ran an MAIC using STARTRK-2 entrectinib data for the ERG's preferred efficacy set and the chemotherapy arm in the ASCEND-4 trial (described in detail in Section 4). The inverse of the estimated HRs from the MAIC were then applied to the modelled entrectinib OS and PFS curve. Time on treatment for PEM+PLAT was assumed to the be 6 cycles in the company's base case.

In a scenario analysis, the company has explored the option of using a cut-off point for the duration of treatment effect with entrectinib for OS and PFS, both together and separately. The company chose to cap treatment effect at 24 months, with the justification that this point in time is where the, "*PFS hazard is stabilised for both entrectinib and crizotinib and censoring becomes high*".

5.3.5.1 ERG critique

The company did not provide any details on the method used to cap the duration of treatment effectiveness with entrectinib in the CS. Inspection of the company's model by the ERG has shown that after 24 months, the company applied the relative risk of events (either OS or PFS, respectively) observed in the PEM+PLAT curve (either estimated with the PROFILE 1014 HR or with the ACEND-4 MAIC HR) to the entrectinib curve. The entrectinib curve was fitted with an exponential distribution,

and the PEM+PLAT curve was derived by applying a HR to the entrectinib or the crizotinib curve depending on the HR chosen (PROFILE 1014 HR is applied to the crizotinib curve while ASCEND-4 MAIC HR is applied to the entrectinib curve). Given that the crizotinib curve was also estimated by applying a HR to the entrectinib curve, all curves in the model are ultimately based on exponential distributions for the entrectinib data (Figure 15 exemplifies OS curves). The implications of this are twofold: the relative risk applied to the entrectinib curve after 24 months (derived as S(t+1)/S(t) from the PEM+PLAT curve) is constant because the PEM+PLAT curves are exponential; and the relative treatment effect between curves does not change after 24 months because even though the RR of events in PFS and OS curves for entrectinib changes to be the same as the RR of events in the PEM+PLAT curve at 24 months, the PEM+PLAT curve itself is estimated by applying the PROFILE 1014 or the ASCEND-4 HR to the entrectinib curve. Therefore, once the entrectinib curve shifts, so do the PEM+PLAT and the crizotinib curves (Figure 16 exemplifies OS curves).

In summary, the ERG disagrees with the company's approach at attempting to cap the duration of treatment effect with entrectinib for both OS and PFS. For that to be achieved, there would have to be some convergence in survival curves, so that the relative treatment effect of entrectinib would be tapered over time.

Figure 15. OS curves without cap on entrectinib's treatment effect

Figure 16. OS curves with 24-month cap on entrectinib's treatment effect

5.3.5.2 Progression-free survival

The company used an exponential model to fit the entrectinib PFS BICR KM data in the ERG's preferred efficacy set (the same distribution was chosen in the company's base case). Figure 17 reports the PFS BICR KM data for entrectinib and the different distributions fitted to the data. The company chose the exponential curve based on its AIC and BIC statistics, and the fact that it provided the most clinically plausible and conservative long-term predictions (5% of patients are progression-free at 5 years). The company also referenced that exponential curves were accepted by the TA529 committee for the extrapolation of PFS data for crizotinib.

To estimate the crizotinib PFS curve, the company used the HR obtained through the MAIC for PROFILE 1001 vs STARTRK-2 (in the ERG's preferred efficacy set). The MAIC HR ([95% CI:]) was inverted ( ) and applied to the entrectinib curve fitted with an exponential model, therefore originating an exponential curve.

Figure 17. ERG's prefrerred efficacy set for entrectinib PFS

Given the paucity of data for the effectiveness of PEM+PLAT in ROS1+ NSCLC patients, the company used ALK+ NSCLC patients as a proxy population to obtain PEM+PLAT PFS data. The company's base case model used the published HR from PROFILE 1014 (2014)[49] and applied it to the estimated crizotinib arm (HR 0.45 [95% CI: 0.35, 0.60]). The inverse of this HR was then applied to the modelled crizotinib PFS curve in the model to estimate the PFS curve for PEM+PLAT (Figure 18).

Figure 18. Entrectinib, crizotinib and PEM+PLAT (PROFILE 1014) PFS curves

After the clarification stage, the company presented an alternative scenario with the MAIC between the entrectinib PFS KM data in the ERG's preferred efficacy set and the chemotherapy arm in the ASCEND-4 trial. In ASCEND-4, ceritinib was compared to platinum-based chemotherapy (pemetrexed plus cisplatin or carboplatin) at first-line followed by pemetrexed maintenance in ALK+ NSCLC patients. The inverse of the estimated HR of [redacted] (95% CI: [redacted]) from the MAIC was then applied to the modelled entrectinib PFS curve, estimating the PFS curve for PEM+PLAT (Figure 19).

The company reported that the key limitation of this approach is the underlying assumption that ROS1 versus ALK gene fusion status is not in itself either prognostic or a treatment effect modifier once imbalances in other patient characteristics have been accounted for. The company added that data on survival outcomes in the entrectinib studies are quite immature with few events observed and median overall survival not reached leading to greater uncertainty in the results.

Figure 19. Entrectinib, crizotinib and PEM+PLAT (PROFILE 1014 and ASCEND-4) PFS curves

5.3.5.3 ERG critique

The ERG agrees that the AIC and BIC statistics for the exponential model indicate a good model fit, but notes that the Weibull and the Gompertz statistics could provide suitable alternatives (company's additional reply to the ERG's clarification questions) and rely on the less strict assumption of varying hazards over time, instead of assuming a constant hazard, implicit with the use of an exponential model. Furthermore, curve selection from previous technology appraisals (TA529 in this case) is not a robust criterion to make model choices, especially when the treatments and the underlying data under consideration are different. Therefore, the ERG ran a scenario analysis to assess the impact of using a Weibull (the next best-fitting curve after the exponential) distribution to fit PFS data for entrectinib in the model.

The ERG has some concerns with the MAIC undertaken to estimate the PFS curves for crizotinib and PEM+PLAT (in the company's scenario analysis), which are discussed in detail in Section 4. As seen in Figure 20, the results of the updated MAIC show that entrectinib is not statistically significantly different from crizotinib in delaying patients' progression, although the trend in KM curves suggests that patients on entrectinib progress faster than patients on crizotinib. The ERG is concerned with the apparent disconnect between the lack of a PFS benefit (potentially a modest detrimental PFS effect with entrectinib) and the survival gains estimated by the company with entrectinib. Clinical expert opinion sought by the ERG supported the anticipated benefit of entrectinib on delaying CNS progression when

compared with crizotinib, however, there are few data to corroborate this CNS advantage over crizotinib, and how this translates into overall disease progression (and ultimately survival). Therefore, the ERG is concerned that the survival benefit with entrectinib is being overestimated in the company's analysis. This issue is further discussed in Section 5.4.5.4.

Figure 20. KM data for BICR PFS (entrectinib vs crizotinib PROFILE 1001 MAIC)

The company reported that the PROFILE 1014 OS and PFS HRs were previously used and accepted for ROS1+ NSCLC patients in TA529. The ERG could not validate this claim through investigation of TA529 documents and asked the company to provide additional details during the clarification stage. The company explained that the OS HR was taken from the latest PROFILE 1014 publication and that data were redacted in the company submission for TA529, but it was noted that a later data cut was used in the latter. The company therefore assumed that this later data cut corresponded to the Solomon *et al* 2018 paper.[50] The PFS HR was taken from a previous publication of PROFILE 1014 data.[49]

Upon inspection of TA529 documents, the ERG concluded that the use of HRs from PROFILE 1014 was not accepted by the TA529 committee. The FAD for TA529 stated that, "*The committee noted the ERG's comments that in both trials* [PROFILE 1014 was one of them], *the proportional hazards assumption* […] *was not valid for progression-free survival so any hazard ratios for progression-free survival should be interpreted with caution. The ERG also highlighted that the overall survival estimates were unreliable because of high rates of crossover, and that statistical methods for adjustment were not reported transparently. The committee agreed that the results showed crizotinib to be more*

effective than chemotherapy for ALK-positive NSCLC, but that its relative effectiveness in ROS1-positive advanced NSCLC remained uncertain."

Therefore, the ERG disagrees with the company's conclusion that the PROFILE 1014 HRs were accepted by the TA529 committee (particularly regarding the concerns around the OS HR – discussed in the next section of the ERG report). Given the conclusion that PHs do not hold for PFS outcomes in PROFILE 1014 and that the committee-accepted analysis in TA529 was based on independently fitted and unadjusted (for cross-over) PROFILE 1014 OS data, the ERG considers the company's rationale flawed. Another limitation, that was acknowledged by the company, of using the PROFILE 1014 HR is that the trial did not include subsequent maintenance treatment with pemetrexed, which the ERG's clinical experts indicated is part of routine clinical practice in the NHS, thus potentially underestimating the effect of pemetrexed compared with current practice.

Furthermore, the ERG considers that some of the company's concerns around using the ASCEND-4 MAIC are somewhat inconsistent. The company states that the approach assumes that gene fusion is not a prognostic factor. The ERG considers there to be no robust evidence to support or oppose using an ALK+ population as a proxy for ROS1+ and therefore assesses results of the MAIC comparing entrectinib in a ROS1+ population to PEM+PLAT in an ALK+ NSCLC with caution. Crucially, there is no way to quantify or adjust for differences in treatment effect that are attributable to the underlying gene fusion (ALK+ or ROS1+). The company also states that data on survival outcomes in the integrated entrectinib studies are quite immature with few events observed and median overall survival not reached leading to greater uncertainty in the results – this argument is true throughout the entire analysis of relative treatment effectiveness presented by the company. Furthermore, ASCEND-4 included maintenance treatment with pemetrexed.

Even though the ERG agrees with the company that the assumptions associated with the base case approach are less strong than those required for the unanchored ASCEND-4 MAIC (because the former retains the benefits of a randomised comparison, and only assumes that the *relative* effect of crizotinib versus PEM+PLAT is similar for ALK+ and ROS1+ NSCLC populations), there is considerable uncertainty around either approach.

The KM data resulting from the company's updated MAIC using the ERG's preferred efficacy set for entrectinib and ASCEND-4 for PEM+PLAT are shown in Figure 21. There is a more plausible relationship between PFS and OS outcomes for entrectinib vs PEM+PLAT compared with PFS and OS outcomes for entrectinib vs crizotinib. Entrectinib shows a statistically significant advantage over PEM+PLAT in delaying patients' disease progression and a non-significant, albeit positive trend, in OS.

Figure 21. KM data for BICR PFS (entrectinib vs PEM+PLAT MAIC)

5.3.5.4 Mortality

The company used an exponential model to fit the entrectinib OS KM data to the ERG's preferred efficacy set (the same distribution was chosen in the company's base case). Figure 22 reports the OS KM data for entrectinib and the different distributions fitted to the data. The company chose the exponential curve based on its AIC and BIC statistics, and the fact that it was deemed to provide the most clinically plausible and conservative long-term predictions. The company also referenced that exponential curves were accepted by the TA529 committee for the extrapolation of OS data for crizotinib.

To estimate the crizotinib OS curve, the company used the HR obtained through the MAIC for PROFILE 1001 vs STARTRK-2 (in the ERG's preferred efficacy set). The MAIC HR ([95% CI:]) was inverted ( ) and applied to the entrectinib curve fitted with an exponential model, therefore originating an exponential curve.

Figure 22. ERG's prefrerred efficacy set for entrectinib OS

The company's base case model used the published HR (adjusted for cross-over) from PROFILE 1014 latest data cut (a later publication than that used for the PFS HR)[50] and applied it to the estimated crizotinib arm (HR 0.346 [95% CI: 0.081, 0.718]) to obtain the OS curve for PEM+PLAT. The rank preserving structural failure time model (RPSFTM) was used to adjust the HR for crossover. The inverse of this HR was then applied to the modelled crizotinib OS curve in the model (Figure 22).

The company's alternative scenario where the MAIC between the entrectinib OS KM data in the ERG's preferred efficacy set and the chemotherapy arm in the ASCEND-4 trial produced an estimated HR of [redacted] (95% CI: [redacted]). The inverse of the HR was then applied to the modelled entrectinib OS curve, estimating the OS curve for PEM+PLAT (Figure 24).

The company's reasoning for preferring the PROFILE 1014 HR to the ASCEND-4 MAIC HR for OS was the same as that given for PFS (section 5.4.5.2). The company added that the OS curve for PEM+PLAT was validated by a clinical expert who agreed that the estimated curve using the HR from the MAIC between the entrectinib and the PEM+PLAT with platinum maintenance from the ASCEND-4 trial resulted in an overly optimistic proportion of patients alive at 5 years (23.8%).

Figure 23. Entrectinib, crizotinib and PEM+PLAT (PROFILE 1014) OS curves

Figure 24. Entrectinib, crizotinib and PEM+PLAT (PROFILE 1014 and ASCEND-4) OS curves

5.3.5.5 ERG critique

The ERG agrees that the AIC and BIC statistics for the exponential model indicate a good model fit, however notes that the Weibull, lognormal and log-logistic statistics could provide suitable alternatives (company's additional reply to the ERG's clarification questions) and rely on less strict assumptions. However, all of the latter portray an even longer survival in the long-term model, therefore the ERG considers that for purposes of clinical plausibility, the exponential distribution is the most conservative choice.

The ERG has some concerns with the MAIC undertaken to estimate the OS curves for crizotinib and PEM+PLAT (in the company's scenario analysis), which are discussed in Section 4. As seen in Figure 25, the results of the updated MAIC show that entrectinib is not statistically significantly different from crizotinib in delaying patients' death, although the trend in KM curves suggests that patients on entrectinib might have a survival benefit compared with crizotinib patients in the longer-term.

Using the ERG's preferred efficacy set, comparing post-progression survival (PPS) for treatment with entrectinib ([redacted] months) and crizotinib (18.48 months), entrectinib yields a [redacted] -month PPS gain. This compares with a PFS "loss" of [redacted] months for entrectinib patients compared to crizotinib patients ([redacted] months for entrectinib vs 23.6 months for crizotinib). This suggests that the treatment benefit with entrectinib only happens after progression (and after patients have stopped treatment) despite patients progressing quicker on entrectinib (Table 20).

This discrepancy is even more accentuated in the company's base case analysis (using the company's preferred analysis set), where the PPS gain with entrectinib is [redacted] months, compared with a PFS "loss" of [redacted] months. These estimates (Table 20) suggest a 3-year survival gain with entrectinib compared with crizotinib, derived only after patients progressed quicker (or arguably at the same time) as crizotinib patients.

Overall, the ERG considers the absolute PFS and OS gains with entrectinib in the company's base case analysis to be clinically implausible, with an overall survival of 7.5 years for entrectinib patients. Nonetheless, it is likely that the crizotinib curves are also overestimated compared with clinical practice, as per clinical expert opinion provided to the ERG. From an incremental perspective (i.e. PFS and OS gains), the ERG also considers the company's base case analysis to produce unsubstantiated results.

Figure 25. KM data for OS (entrectinib vs crizotinib PROFILE 1001 MAIC)

Table 20. PFS, PPS and OS gains (undiscounted)

Analysis set	Treatment	PFS months	PPS months	OS months
ERG's preferred efficacy set	Entrectinib	[redacted]	[redacted]	[redacted]
	Crizotinib	23.60	18.48	42.08
	PEM+PLAT PROFILE1014	10.69	3.87	14.57
	PEM+PLAT ASCEND-4	10.43	27.78	38.21
	Entrectinib vs crizotinib	[redacted]	[redacted]	[redacted]
	Crizotinib vs PEM+PLAT PROFILE 1014	12.90	14.61	27.51
	Crizotinib vs PEM+PLAT ASCEND-4	13.17	-9.30	3.87
Company's base case	Entrectinib	[redacted]	[redacted]	[redacted]
	Crizotinib	26.44	26.47	52.91
	PEM+PLAT PROFILE1014	11.98	6.35	18.33
	PEM+PLAT ASCEND-4	10.56	31.19	41.74
	Entrectinib vs crizotinib	[redacted]	[redacted]	[redacted]
	Crizotinib vs PEM+PLAT PROFILE 1014	14.46	20.12	34.58

	Crizotinib vs PEM+PLAT ASCEND-4	15.88	-4.72	11.16

In TA529, a less extreme, but comparable situation between crizotinib and PEM+PLAT was assessed by the respective ERG. The ERG pointed to the fact that the PPS gain with crizotinib (19.2 months) compared with a PFS gain of 9.5 months with PEM+PLAT and considered this modelled outcome to not be supported by the evidence from the trials nor by the literature. The ERG added that, "*There is evidence to suggest that it is plausible to assume (in the absence of robust evidence to the contrary) that the OS treatment effect might be expected to be similar to the PFS treatment effect in advanced NSCLC trials.* […] *the ERG in TA422 referred to an analysis by the FDA78 which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib). The results of this analysis suggest that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence. The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, not least because a substantial proportion of patients in the PROFILE 1014 trial continued to receive crizotinib after progression due to 'symptomatic benefit' (mean length of post-progression treatment in the model is 1.4 months). However, given that the magnitude of OS gain is unknown in the PROFILE 1014 trial due to trial immaturity and patient crossover, the ERG considers it questionable to model a PPS gain that is substantially larger than PFS gain (which translates into a greater OS treatment effect than PFS treatment effect*)."

The appraisal consultation document (ACD) for TA529 concluded, "*The clinical experts explained that progression-free survival gains would be expected to result in some overall survival benefit, but the exact relationship is difficult to predict. Nevertheless, the experts agreed that a modelled overall survival gain almost 3 times higher than the modelled progression-free survival gain was most likely to be overestimate. The committee agreed that it had seen no evidence to support the large disparity between overall and progression-free survival.*"

The final appraisal determination (FAD) concluded that, "[…] *the overall survival gain for crizotinib was somewhere between the company's new scenario analyses using the lower bounds of clinical benefit (that is, an overall survival benefit of 13.1 months for untreated disease and 16.2 months for previously treated and the ERG's estimates assuming no benefit in the progressed state, but reiterated that this analysis was still based on a proxy population and therefore considerable uncertainty remained.*"

In light of the discussions in TA529 around the relationship between PFS and OS gains, the ERG highlights that similar issues are present in the current submission for entrectinib compared with crizotinib. Even if the PFS results for entrectinib vs crizotinib are interpreted as reflecting a similar PFS gain across treatments, the survival gain with entrectinib is still implausibly high in the company's base

case (36.6 months). Furthermore, STARTRK-2 is a single arm, small study, with very immature OS data, and both the PFS and OS MAIC analyses have shown non-statistically significant results for entrectinib compared with crizotinib. The issues in the current submission are aggravated by the fact that there are no trials comparing entrectinib with crizotinib to validate modelled results (although [redacted]

In order to explore some of the uncertainty around the OS benefits for entrectinib vs crizotinib, the ERG conducted scenario analysis. The ERG has not heard from clinical experts that the PFS results favouring crizotinib vs entrectinib are expected in clinical practice, and so these could potentially be attributable to the inaccuracy of the MAIC results due to low statistical power or unadjusted for confounding factors. Furthermore, the ERG in TA422 referred to an analysis by the FDA which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib), suggesting that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence. Therefore, the ERG conducted sensitivity analysis assuming a PFS HR=1 and an OS HR =1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression and extending life.

The ERG has several concerns with the company's use of the RPSFTM-adjusted OS HRs from the latest data cut-off from PROFILE 1014. The ERG report in TA529 stated (in reference to PROFILE 1014) that, "*…the company's RPSFTM method of adjusting for the impact of treatment switching is flawed and that, as such, the company's crossover-adjusted HR is unreliable.* […] *the ERG is also unsure whether the RPSFTM method is appropriate for adjusting for crossover, since the RPSFTM, and indeed the IPE, assumes a "common treatment effect", i.e., that the treatment effect received by patients who switch must be the same as the treatment effect received by patients initially randomised to the experimental group. The ERG notes that it is unclear whether this assumption would hold since patients randomised to pemetrexed+platinum who switch to crizotinib may, at that time, have more advanced disease than patients who were originally randomised to crizotinib; the patients randomised to pemetrexed+platinum, therefore may not have the same capacity to benefit from crizotinib treatment following disease progression as patients randomised to crizotinib. The ERG recognises that it is not possible to test the "common treatment effect" assumption, and that, in practice, this assumption is highly unlikely to ever be exactly true."* The ERG report in TA529 concludes that, "*In summary, the ERG considers that there is no method of adjusting for treatment switching that the ERG can confidently conclude would generate unbiased OS risk estimates for crizotinib versus chemotherapy for patients in the PROFILE 1014 trial.* [and that] *The ERG prefers to accept the level of crossover (19.2%) rather than use the company's RPSFTM-adjusted curve, as the company's RPSFTM-adjusted curve for treatment with crizotinib in the first-line model estimates better survival for crizotinib than the*

unadjusted curve. The ERG has not seen the details of the company's crossover methods and therefore cannot comment on the approach."

At the time of TA529, the PROFILE 1014 OS data were more immature than the crizotinib data used by the company in the entrectinib submission. Therefore, while the ERG in TA529 preferred to accept the level of cross-over of 19.2% of patients and use the unadjusted OS data, the updated PROFILE 1014 data is based on 84% of patients crossing over from PEM+PLAT to crizotinib.

The OS HRs from PROFILE 1014 are marked confidential in TA529, and the ERG could not find the unadjusted OS HR in any published papers based on the earliest data cut for the trial. Furthermore, the latest PROFILE 1014 OS publication reports an unadjusted HR of 0.760 (95% CI: 0.548 to 1.053), which compares to the adjusted HR of 0.346 (95% CI: 0.081, 0.718). However, the proportion of patients crossed over at the latest data cut-off reached 84% and so the ERG does not consider that the use of the unadjusted HR is a robust option.

In summary, the ERG considers that both approaches presented by the company to estimate OS for PEM+PLAT have considerable flaws. Nonetheless, given the conclusions in TA529 that the maximum expected survival benefit of crizotinib vs PEM+PLAT would be between 13 and 16 months; and the modelled results presented in Table 20; where using the PROFILE 1014 HR in the ERG's preferred efficacy set yields a survival benefit of 27.5 months for crizotinib and using the ASCEND-4 MAIC HR produces a survival benefit of 3.9 months, the ERG considers that using the ASCEND-4 MAIC produces more conservative results. The ERG undertook sensitivity analysis reporting final results using both approaches.

5.3.5.6 Time to treatment discontinuation

The company used an exponential model to fit the entrectinib ToT KM data in the ERG's preferred efficacy set (the same distribution was chosen in the company's base case). Figure 26 reports the ToT KM data for entrectinib and the different distributions fitted to the data. The company chose the exponential curve based on its AIC and BIC statistics, and the fact that it was deemed to provide the most clinically plausible and conservative long-term predictions (median ToT of 15.77 months).

The company assumed that ToT with crizotinib is the same as PFS, thus assuming that treatment is given till progression. For PEM+PLAT, the company assumed that treatment lasts for 6 weeks and referred to the SmPC and TA529 to justify the assumption. The company also undertook sensitivity analysis assuming 4 weeks of treatment with PEM+PLAT.

Figure 26. ERG's prefrerred efficacy set for entrectinib time on treatment

5.3.5.7 ERG critique

Similar to PFS outcomes, the ERG agrees that the AIC and BIC statistics for the exponential model indicate a good model fit, however notes that a Weibull or a Gompertz distribution could also provide a good fit to the data and rely on less strict assumptions than the exponential model (constant hazard over time).

During the clarification stage, the company explained that ToT data collected on entrectinib was estimated as (last dose day – first dose day +1)/30.5. The company added that death was not censored, and that for patients still on therapy at the data cut-off date, the last dose day was set at the clinical cut-off date. Figure 27 shows the PFS and ToT KM data for the ERG's preferred efficacy set. The data show that for the follow-up period, most patients discontinued treatment at the same time, or after progression. Figure 28 shows both the ToT and the PFS fitted exponential curves, which reflect the underlying KM data, portraying a scenario where most patients discontinue treatment after, or at the same time of progression. The majority of patients (55% patients) in the ERG's preferred efficacy set (n=78), [redacted], and [redacted] discontinued treatment [redacted] (Table 21).

While the fitted exponential curves show that ToT was generally longer than time to progression, other distributions such as the Weibull or the Gompertz, show a bigger ToT and PFS separation (Figure 29). Given the apparently better clinical plausibility of the Weibull tail, the ERG ran a scenario analysis using a Weibull curve to fit ToT and PFS in the economic model. Results are reported in section 6.

Figure 27. Entrectinib ToT and PFS KM data - ERG's preferred efficacy set

Figure 28. Entrectinib ToT and PFS fitted exponential curves - ERG's preferred efficacy set

Table 21. Entrectinib ToT and PFS events - ERG's preferred efficacy set

ToT status	PFS status	Comparison	n
Censored	Censored	ToT < PFS	[redacted]
Censored	Censored	ToT = PFS	[redacted]
Censored	Censored	ToT > PFS	[redacted]
Censored	Event	ToT = PFS	[redacted]
Censored	Event	ToT > PFS	[redacted]
Event	Censored	ToT < PFS	[redacted]
Event	Censored	ToT = PFS	[redacted]
Event	Censored	ToT > PFS	[redacted]
Event	Event	ToT < PFS	[redacted]
Event	Event	ToT = PFS	[redacted]
Event	Event	ToT > PFS	[redacted]

Key: CCOD, clinical cut-off date; PFS, progression-free survival; ToT, time on treatment

Figure 29. Entrectinib ToT and PFS fitted Gompertz and Weibull curves - ERG's preferred efficacy set

The company's assumption that crizotinib is given until disease progression is not unreasonable. Even though there is a clinical argument for treating patients beyond progression with crizotinib (when clinical benefit is still derived, and no other alternative treatments are available), the company's approach is conservative, in that it doesn't assume treatment costs with crizotinib beyond progression.

To note is that PFS for crizotinib in the company's model (both with the company's data set and the ERG's preferred data) is longer than PFS and ToT for entrectinib (as discussed in Section 5.4.5.2), therefore treatment costs for crizotinib are higher than treatment costs with entrectinib in the analysis (Figure 30).

Figure 30. ToT with entrectinib and crizotinib (PFS proxy)

The ERG notes that TA529 used time to treatment discontinuation (TTD) data from PROFILE 1014 to estimate treatment duration with PEM+PLAT and did not use the 4 to 6 cycles assumption as suggested by the company. Nevertheless, the ERG's clinical experts agreed with the company's assumption for the current submission but pointed out that 4 cycles of treatment is more common than 6 cycles of PEM+PLAT. Furthermore, clinical expert opinion provided to the ERG advised that maintenance treatment with pemetrexed is often given until disease progression. These issues are further explored in Section 5.3.8 of the ERG report.

5.3.6 Adverse events

The company included the impact on both costs and utilities of adverse events (AEs) associated with each of the primary treatments evaluated in the economic model. For entrectinib, the proportion of patients experiencing AEs was taken from the company's preferred efficacy set and was based on Grade 3 and 4 AEs. For crizotinib, data were taken from the PROFILE 1001 trial and for PEM+PLAT data were taken from PROFILE 1014.[46, 50] However, the company did not state whether any restrictions were applied to the PROFILE 1001 or 1014 data, e.g. by grade, by a percentage threshold, or whether they were treatment-related or treatment-emergent AEs. The proportion of patients expected to experience each of the included AEs in the economic is given in Table 22.

Table 22. Adverse events used in the company's economic model (CS, page 134, Table 44)

Adverse events	Entrectinib arm ALKA/ STARTRK-1/2 (N=53)	Crizotinib arm PROFILE 1001 (N=53)	Pemetrexed plus platinum PROFILE 1014 (N=171)
Anaemia	[redacted]	0.0%	8.9%
Arthralgia	[redacted]	0.0%	0.0%
Elevated Transaminases	[redacted]	0.0%	2.3%
Hypophosphatemia	[redacted]	13.2%	0.0%
Leukopenia	[redacted]	0.0%	5.3%
Myalgia	[redacted]	0.0%	0.0%
Neutropenia	[redacted]	9.4%	15.4%
Pulmonary embolism	[redacted]	0.0%	6.5%
Thrombocyte	[redacted]	0.0%	6.5%
Weight increased	[redacted]	0.0%	0.0%

5.3.6.1 ERG critique

The ERG cross-checked the values applied in the economic model and noted that the values used for crizotinib do not match the values reported in the key paper relating to the safety population from PROFILE 1001. Shaw *et al.* 2019 reported treatment-related AEs by any grade where at least 10% of patients had experienced the event. The grade 3 AEs were also presented for this set of AEs and the author noted that no grade 4 AEs were reported. Grade 3 hypophosphataemia was recorded in 8 of the 53 patients (15.1%), whereas the company appear to have assumed 7 (13.2%). The neutropenia value the company have used is the same as that reported in Shaw *et al.* 2019 but for elevated transaminases, Shaw *et al.* 2019 reports that 2 patients (3.8%) experienced this event with grade 3 severity in contrast to the company's value of zero. Nausea and decreased appetite were reported in 1 patient (1.9%) each and vomiting in 2 patients (3.8%) but none of these were captured in the company's model. The ERG tested the impact on the company's base case ICER by using the correct values for hypophosphataemia and elevated transaminases and found that it had a negligible impact on the ICER. The ERG considers it likely that the other reported AEs that were not captured in the company's model would also have a negligible impact and, therefore, the ERG does not have concerns regarding the company's exclusion of these.

The ERG is concerned with the assumptions around pulmonary embolism rates in the model. The company assumed that 6.5% of PEM+PLAT patients experienced pulmonary embolism in the model (based on PROFILE 1014 data). However, the Solomon *et al.* 2014 study does not report any pulmonary embolism events. Furthermore, the company assumed that 0% of patients in the crizotinib arm experienced pulmonary embolisms, but this was based on PROFILE 1001 data. Nonetheless, within the tables of figures in the model (but not used in the analysis) it was reported that 6.43% of crizotinib patients experienced a pulmonary embolism in PROFILE 1014 data. Given that the ERG could not

verify the rates of pulmonary embolisms in PROFILE 1014, and that 0% of entrectinib patients were assumed to have pulmonary embolisms in the model, a scenario analysis was undertaken to remove the PEM+PLAT events in the model to avoid a potential bias against PEM+PLAT. This scenario had only a small impact on the company's base case ICER (using the ERG's preferred efficacy set), increasing it from £21,057 to £21,302 per QALY gained. In comparison to the corrected base case reported in Section 6.1, which applies a correction to the AE management costs, the impact of this becomes even smaller as the costs of pulmonary embolism are greatly reduced.

5.3.7 Health-related quality of life

Utility data were collected in the STARTRK-2 trial using the EuroQoL 5-dimension questionnaire with 3 scoring levels (EQ-5D-3L). All patients were asked to complete the EQ-5D-3L on the first day of the first cycle of treatment, and then on the first day of each subsequent treatment cycle and at the end of treatment. The company presented a summary of the data obtained from the trial at baseline, and by progression status.

As a result of the clarification stage, the company provided a summary of utility values in STARTRK-2 for the ERG's preferred efficacy set. This dataset provided utility data for [redacted] patients and is summarised in Table 23. The company also provided a summary of utility values used in the company's preferred efficacy set, reported in Table 24.

Table 23. Utility data from the ERG's preferred efficacy set (Adapted from Table 32 of the company's response to clarification)

State	N	Mean	SD
Baseline	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of patients; SD, standard deviation.

Table 24. Summary of ROS1 utilities from STARTRK-2 (Adapted from Table 32 of the company's response to clarification)

State	N	Mean	SD
Baseline	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of patients; SD, standard deviation.

To estimate PFS utility values to be used in the model, the company fitted a linear mixed model to the PFS utility data and used a backwards stepwise selection procedure to determine which variables to include. This model was performed using the *lmer* package in *R* and the default significant thresholds for inclusion of variables were used, that is, p-values of 0.05 for fixed effects and 0.1 for random effects. The selection procedure began with age, sex, extent of metastasis and time from the start of treatment as fixed effects, all of which were excluded after completion of the selection procedure. The company

included the slope and intercept as random effects in the model and the resulting estimated health state utility value (HSUV) for the PFS health state was 0.73. The company assumed that all treatment groups would have the same HSUV for the PFS health state, and they considered this a conservative assumption. However, no further justification was provided to support this assumption.

For the PPS health state, the company used an alternative data source to inform the utility, as they did not consider there to be sufficient data post progression from the STARTRK-2 trial to provide a reliable estimate. The company did not identify any additional sources of utility data in a ROS1+ population. Therefore, the company chose to use the HSUVs that were used in TA529, which were sourced from the PROFILE 1007 trial with a population of ALK+ NSCLC patients whose disease had progressed after first-line treatment.[51] The utilities for each treatment and each health state used in the model are summarised in Table 25. To note is that the regression-estimated PFS utility was the same in the company's and in the ERG's preferred efficacy set.

Table 25. Summary of utilities used in the company's base case

Treatment	PFS utility	PPS utility
Entrectinib	0.73	0.66
Crizotinib	0.73	0.66
Pemetrexed plus platinum	0.73	0.66

The impact of AEs on HRQoL was estimated using utilities derived from two studies: Doyle *et al.* 2008 and Nafees *et al* 2008.[52, 53] These were used in combination with AE rates captured in the trials used to inform treatment effectiveness. Doyle *et al.* 2008 conducted a study in which 101 metastatic lung cancer patients were interviewed and completed a standard gamble tool to elicit utilities relating to different disease states and symptoms. A mixed model was used to estimate these values. Nafees *et al.* conducted a study in which a sample from the general population were interviewed to elicit utilities associated with the likely impact of adverse events, which were described to the participants by clinicians. Participants were asked to rate 12 health states using a standard gamble technique, after which the data were used to fit a mixed effects model to estimate the impact of each adverse event on utility values. The utilities used from these data sources to inform the company's base case analysis are given in Table 26.

Table 26. Utility decrements used by company (adapted from CS, Page 135, Table 45)

Adverse events	Utility decrement	Source
Anaemia	0.073	Nafees *et al.* 2008
Arthralgia	0.012	Doyle *et al.* 2008
Elevated transaminases	0.000	Doyle *et al.* 2008
Hypophosphatemia	0.000	Doyle *et al.* 2008
Leukopenia	0.090	Nafees *et al.* 2008

Myalgia	0.131	Doyle *et al.* 2008
Neutropenia	0.090	Nafees *et al.* 2008
Pulmonary embolism	0.012	Doyle *et al.* 2008
Thrombocyte	0.000	Nafees *et al.* 2008
Weight increased	0.000	Doyle *et al.* 2008

These utilities were used to estimate a one-off QALY decrement associated with each treatment by multiplying the decrements estimated in the Nafees *et al.* model by the proportion of patients who experienced each of the adverse events in the relevant trials. For entrectinib, this was based on grade 3 and 4 AEs observed in the integrated trial analysis in the company's original base case. For crizotinib and PEM+PLAT, data were sourced from PROFILE 1001 and 1014, respectively. The one-off QALY decrements applied in the model are given in Table 27.

Table 27. QALY decrements applied in the model (CS, Page 135, Table 46)

Treatment arm	QALY decrement
Entrectinib	0.001221061
Crizotinib	0.000694993
Pemetrexed plus platinum	0.002126286
Abbreviations: QALY, quality-adjusted life year.	

5.3.7.1 ERG critique

The ERG notes, firstly, that the company's preferred efficacy set analysis of utility data was based on a small sample of just [redacted] patients. The utility values derived in the ERG's preferred efficacy set ([redacted] patients) values appear to be slightly lower than those used by the company, and more importantly, the difference between the PFS value and the PPS value is higher than that in the company's analysis. This means that any PFS gain has a bigger impact on the total QALY gain in the ERG's preferred set.

With regard to the analysis of utility data, the company provided very little detail in the CS to describe their approach to the analysis. In response to clarification questions, the company provided the coefficients of each variable at each stage of the selection procedure for the mixed regression model but did not provide p-values to show how robust each estimate was for each stage. The ERG considers that given the limited data even in the ERG's preferred efficacy set, it is unlikely for any of the coefficients to be significant at the default significance thresholds, so the exclusion of all fixed effects is not unexpected. However, the ERG would have liked to see how close these p-values were to the thresholds for inclusion.

In response to clarification questions, the company provided the R code used to run the analysis, which gave some more clarity to the company's approach. The ERG notes that the company applied a restricted maximum likelihood estimation (REML) approach to the mixed model. This means the mixed model was fitted in a two-stage approach in which only the random-effects were included in the model

initially, and then the fixed effects were included on top of the resulting random effects model to account for the remaining variance not explained by the random effects.

The ERG considers that from a methodological point of view the company's approach is reasonable, however, it is concerned that the company have not implemented the results of the regression model correctly. The resulting model includes only random effects for time from first assessment and for the intercept, as all fixed effects had p-values greater than 0.05 and were therefore excluded. To implement the company's final random-effects regression model requires a coefficient for the time from first assessment as well as a value for the intercept; neither of these values appear to have been provided by the company. The standard summary output of this regression model in R does not provide estimates of the random-effects coefficients as there is an estimate for each individual in the dataset. Therefore, the mean of these estimates needs to be calculated and those values should be used to calculate the HSUV inputted into the economic model.

Further to this, the ERG is unclear why the company chose the [redacted] utility value as this was the fixed effect intercept that was estimated as part of the selection procedure in the second stage of the regression model, where all fixed effects were excluded in the selection procedure. The company's estimate of the HSUV for the PFS health state is therefore flawed, and the ERG disagrees with its use in the economic analysis.

The lack of data beyond progression means that it is unlikely that a regression model would have provided more robust and reliable estimates than simply using the raw mean estimates observed in the trial (Table 23) without accounting for time from baseline or the correlation between that time and the baseline utility.

Furthermore, the ERG considers it a potentially serious limitation to use different data sources to inform different health states in the economic model, as there is a correlation between health state values that is lost with this approach, and the relationship between the values of each health state are likely to be a more influential driver in the economic model than the baseline utility scores. Therefore, the ERG ran a scenario analysis using the company's raw mean utility values of [redacted] for PFS and [redacted] for PPS and reports the results in Section 6.

In response to the ERG's clarification questions, the company provided a range of scenario analyses to test the impact of using alternative but consistent data sources to inform the HSUVs for the PFS and PPS health states. The ERG requested that PROFILE 1007, PROFILE 10014 and ALEX[54] were used to inform utility values in the model, and the company provided the scenario analyses given in Table 28.

Table 28. Alternative utility values used in the company's scenario analyses (Adapted from Table 35 of the company's response to clariifcation)

c	Utility values used	Source
Base case	PFS: 0.73 PPS: 0.66	STARTRK-2 PROFILE1007 (reported PFS utility for patients on chemotherapy)
a)	PFS: 0.82 PPS: 0.61	PROFILE1007 (Blackhall *et al.* 2014[55]) PROFILE1007 (TA296 reappraisal committee papers, page 16)[56]
	PFS: 0.82 PPS: 0.47	PROFILE1007 Nafees *et al.* 2008
b)	PFS: 0.81 PPS: 0.66	PROFILE1014 (TA529 FAD)[12] TA406[57]
c)	PFS: 0.81 PPS: 0.73	ALEX (TA536, ERG report, Table 21)[58]
	PFS: 0.81 PPS: 0.65	ALEX Roughley *et al.* 2014[6] (preferred PPS utility by committee in TA536)
Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal; FAD, final appraisal determination.		

The company's reporting of utility values in this scenario analysis was somewhat unclear. In particular, the PPS utility from PROFILE 1007, which the company sourced originally for their base case from the committee papers for TA529 with a value of 0.66, was also stated in the committee papers for TA422 – the update for TA296 – to have a value of 0.61 as per the original appraisal. Therefore, the company provided a scenario with 0.61 as the PPS HSUV along with the PFS value of 0.82. However, the documentation for the original appraisal is no longer publicly available so the ERG could not validate whether this value was the value used in the original appraisal. The company also provided another scenario relating to PROFILE 1007 in which they applied a value of 0.47 for the PPS HSUV; however, the ERG notes that this value relates to third-line patients who are receiving best supportive care. The ERG considers the most relevant values for a scenario using only PROFILE 1007 to inform all HSUVs are 0.82 for PFS and 0.66 for PPS, as stated in the committee papers for TA529. The company did not perform this analysis, so the ERG has conducted this as a scenario analysis and reports the results in Table 29 below.

For the scenario using the HSUV from ALEX, the company took data from the ERG report for TA536. In this appraisal, the committee preferred the use of an alternative data source for the PPS HSUV, so the company has provided scenarios using the original values as well as the committee's preferred values. The results of each of these scenarios are provided in Table 29.

The results from the scenario analysis undertaken by the company show that using different utility estimates for PFS and PPS can have a considerable impact on the final ICERs, mainly for entrectinib vs PEM+PLAT. The ERG considers the use of the raw mean utility values estimated directly from the ERG's preferred efficacy set to be preferable to the company's analysis (even if it does not capture the impact of potential changes over time that may be observed in the repeated measures). This scenario

([redacted] for PFS and [redacted] for PPS), together with the utility values accepted in TA529 (PFS=0.81; PPS=0.66) are explored in Section 6 of this report.

Table 29. Results of company's utility scenario analysis using ERG's preferred efficacy set

	Utility values used	Source	ICERs
Base case	PFS: 0.73 PPS: 0.66	STARTRK-2 PROFILE1007 (reported PFS utility for patients on chemotherapy)	Entrectinib vs PEM+PLAT £21,057
			Entrectinib vs crizotinib Entrectinib dominant
a)	PFS: 0.82 PPS: 0.61	PROFILE1007 (Blackhall *et al.* 2014) PROFILE1007 (TA296 reappraisal committee papers, page 16)	Entrectinib vs PEM+PLAT £21,560
			Entrectinib vs crizotinib Entrectinib dominant
	PFS: 0.82 PPS: 0.47	PROFILE1007 Nafees *et al.* 2008	Entrectinib vs PEM+PLAT £25,663
			Entrectinib vs crizotinib Entrectinib dominant
b)	PFS: 0.81 PPS: 0.66	PROFILE1014 (TA529 FAD) TA406	Entrectinib vs PEM+PLAT £20,466
			Entrectinib vs crizotinib Entrectinib dominant
c)	PFS: 0.81 PPS: 0.73	ALEX (TA536, ERG report, Table 21)	Entrectinib vs PEM+PLAT £19,094
			Entrectinib vs crizotinib Entrectinib dominant
	PFS: 0.81 PPS: 0.65	ALEX Roughley *et al.* 2014 (preferred PPS utility by committee in TA536)	Entrectinib vs PEM+PLAT £20,661
			Entrectinib vs crizotinib Entrectinib dominant
ERG's scenario	PFS: 0.82 PPS: 0.66	PROFILE1007 PROFILE1007	Entrectinib vs PEM+PLAT £20,395
			Entrectinib vs crizotinib Entrectinib dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal; FAD, final appraisal determination.

Another concern the ERG had was that the disutilities associated with AEs used for the model were sourced from a study that used a different elicitation technique to the NICE-preferred method of the EQ-5D as outlined in the NICE Guide to the Methods of Technology Appraisal 2013.[59] As well as the elicitation tool not aligning with the NICE-preferred approach, in the studies used for AE disutilities and with the HSUVs applied in the economic model, the tool was not used directly with patients with ROS1+ NSCLC but instead was used with healthy volunteers who relied on descriptions of symptoms from clinicians. This means that the two key aspects of the EQ-5D have not been adhered to. That is, the health states were not described by the patient and those health states were not valued by the general public using the time trade-off technique.

Although the ERG considers this to be a limitation of the analysis, the ERG notes the limited data available and considers it unlikely that the company could have identified a better source of data. Furthermore, the ERG ran a scenario to remove the AE disutilities and found that the company's base case ICER (using the ERG's preferred efficacy set) increased by only £10. Therefore, this issue is relatively minor in comparison to other issues and is not a key source of uncertainty in the company's analysis.

5.3.8 Resources and costs

The company stated that their model is populated with costs that are reflective of the UK NHS perspective and include drug acquisition, monitoring, end-of-life (EoL) care, adverse event (AE) management, ROS1-positive NSCLC testing and subsequent treatment costs. Each of these are described in turn in the following subsections.

5.3.8.1 Acquisition costs

For all branded products, acquisition costs were taken from the Monthly Index of Medical Specialties (MIMS),[60] while for generic products, prices were taken from the Electronic Market Information Tool (eMIT).[61] Details of the dose required per treatment cycle and the associated cost per cycle for each of the relevant drugs compared in the economic analysis are given in Table 30. The company has proposed a simple PAS with a discount of [redacted] on the list price. The costs with and without this PAS applied are both given Table 30.

Table 30. Unit costs of entrectinib and comparators

Treatment	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Entrectinib	600mg per day (30 days)	[redacted]
Crizotinib	500mg per day (30 days)	£4,689.00
Pemetrexed	500mg/m^2 once every 3 weeks	£1,418.60
Cisplatin	75mg/m^2 once every 3 weeks	£11.37
Carboplatin	AUC 5-6 resulting in 536.49 (based on the Calvert formula)	£15.68

Abbreviations: AUC, area under the curve; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; PAS, patients access scheme.

In addition to acquisition costs, the company included costs associated with administering each of these treatments. Entrectinib and crizotinib are both taken orally and therefore do not require any hospitalisation for administration. The company assumed there to be an initial cost associated with these treatments in the first treatment cycle, equivalent to the cost of delivering oral chemotherapy from NHS

Reference Costs 2017/2018,[62] with a value of £141. In each treatment cycle after this, the company assumed that only a dispensing cost would be incurred, and this was estimated as 12 minutes of a pharmacist's time with a cost of £15 based on unit costs from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2018.[63]

For PEM+PLAT, administration costs were greater as hospitalisation is required to deliver the treatment regimens intravenously. The costs of administration were sourced from NHS Reference Costs 2017/2018. The cost description for the Health Resource Group (HRG) used for the first treatment cycle was, "*Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance"*, while subsequent treatment cycles were assumed to have a cost associated with the HRG with cost description, *"Deliver Subsequent Elements of a Chemotherapy"*. Administration costs for each treatment are summarised in Table 31.

Table 31. Drug administration costs

Treatment	Model cycle	Setting	HRG cost code	Description	Unit cost
Entrectinib and crizotinib	First cycle	Oral	SB11Z	Deliver Exclusively Oral Chemotherapy	£140.82
	Thereafter		NA	Dispensing cost (12 minutes pharmacist time)	£14.59
Pemetrexed plus cisplatin/carboplatin	First cycle	IV	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£337.00
	Thereafter		SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	£289.00

Abbreviations in table: HRG, Health Resource Group; IV, intravenous; NA, not applicable.

To estimate the proportion of patients who remain on treatment at any given cycle, and thus continue to incur drug acquisition and administration costs, the company used ToT data from relevant trials where available. For entrectinib, the company used ToT data from the company's preferred efficacy set for their initial base case as described in the CS. In response to clarification questions, the company also provided an equivalent analysis using the ERG's preferred efficacy set to inform ToT.

For crizotinib there was no ToT data available to inform the proportion of patients expected remain on treatment over time, and therefore, the company assumed that patients would be treated until progression.

For PEM+PLAT, the company assumed that all patients would receive 6 cycles of treatment, which is in line with the SmPC and TA529.[12, 64] The SmPC states that between 4 and 6 cycles of chemotherapy can be given, and therefore, the company performed a scenario analysis in which only 4 cycles of pemetrexed plus platinum were applied.

5.3.8.2 Health state costs

As well as the costs associated with delivering each of the treatments, the company also included costs associated with general monitoring of disease and effects of treatment. These included diagnostic tests, imaging, and various appointments with different health care specialists, assumed to have different resource requirements in the PFS state compared to the PPS health state.

The company sourced resource estimates from the NICE technology appraisal for crizotinib in patients with ROS1+ NSCLC (TA529). The company stated that the same estimates were also used in other NICE crizotinib appraisals for untreated and previously treated patients with ALK+ NSCLC (TA406 and TA422, respectively),[57, 65] and for the NICE appraisal of erlotinib for first-line treatment of locally advanced or metastatic, epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, NSCLC (TA258).[66] The resource requirements assumed for each health state, and their associated costs, are summarised in Table 32.

Table 32. Health state resource use and costs (adapted from Table 50 on pages 144-145 of the CS)

	Resource required	% patients per month	Frequency per month	Frequency per model cycle (30 days)	Unit cost	Reference for unit cost
Progression-free	Outpatient visit	100%	0.75	0.74	£162	NHS Reference costs 2017-18, outpatient attendance - medical oncology (370)
	GP visit	10%	1.00	0.10	£28	PSSRU 2018- Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	20%	1.00	0.20	£89	NHS Reference costs 2017-18, Nurse cancer relate adult face to face (N10AF)
	Complete blood count	100%	0.75	0.74	£3	NHS Reference costs 2017-18, Direct access: pathology services (DAPS05)
	Biochemistry	100%	0.75	0.74	£1	NHS Reference costs 2017-18, Direct access: pathology services (DAPS04)
	CT scan	30%	0.75	0.22	£133	NHS Reference costs 2017-18, Three areas, with contrast (RD26Z)
	Chest X-ray	30%	0.75	0.22	£31	NHS Reference costs 2017-18, direct Access plain film (DAPF)
	Total cost per cycle (30 days)				**£179**	
Progressed	Outpatient visit	100%	1.00	0.99	£162	NHS Reference costs 2017-18, outpatient attendance - medical oncology (370)
	GP visit	28%	1.00	0.28	£28	PSSRU 2018- Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	10%	1.00	0.10	£89	NHS Reference costs 2017-18, Nurse cancer relate adult face to face (N10AF)
	Complete blood count	100%	1.00	0.99	£3	NHS Reference costs 2017-18, Direct access: pathology services (DAPS05)
	Biochemistry	100%	1.00	0.99	£1	NHS Reference costs 2017-18, Direct access: pathology services (DAPS04)
	CT scan	5%	0.75	0.04	£133	NHS Reference costs 2017-18, Three areas, with contrast (RD26Z)
	Chest X-ray	30%	0.75	0.22	£31	NHS Reference costs 2017-18, direct Access plain film (DAPF)
	Total cost per cycle (30 days)				**£192**	

Abbreviations: CT, computed tomography; GP, General practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

5.3.8.3 Palliative care costs

A one-off cost of £8,756, representing hospital care received by patients who are in the final stages of life, was applied in the model to all patients at the point of death. This cost was taken from a study by Georghiou and Bardsley 2014 and includes various nursing and inpatient care costs associated with palliative treatment in the end stages of life.[67] The company inflated the costs from 2014 prices to 2018 prices using the PSSRU inflation indices.[63] The breakdown of costs that are included in the total cost are given in Table 33.

Table 33. Breakdown of palliative care costs

Cost	Unit cost	2017/18 Uplifted cost (PSSRU 2018)[63]
District nurse	£278	£353
Nursing and residential care	£1,000	£1,285
Hospital care – inpatient	£550	£699
Hospital care – final 3 months of life	£4,500	£5,719
Marie Curie nursing service	£550	£699
Total		**£8,756**
Abbreviations: PSSRU, Personal Social Services Research Unit.		

5.3.8.4 Adverse event management costs

The company sourced unit costs for the management of adverse events (AEs) from NHS reference costs 2017/2018. Assumptions regarding resource use required to manage each of the adverse events were aligned with those used in TA529, and the company noted specifically that leukopenia, neutropenia and elevated transaminase were assumed to incur no costs as they would be expected to be managed by dose reductions. The unit costs used along with the specific sources are given in Table 34.

Table 34. Unit costs for the management of adverse events

Adverse events	Hospitalisation days required	Unit Costs	Source
Anaemia	1.7	£294	NHS reference costs 2017/18; Iron Deficiency Anaemia with CC Score 0-1 SA04L(day case)
Arthralgia	1	£162	NHS reference costs 2017-18 Medical oncology 370 (TA529 assumption)
Elevated transaminases	-	-	Managed by dose reduction (as per TA529 assumption)
Hypophosphatemia	1.7	£309	NHS reference costs 2017/18; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Leukopenia	-	-	Managed by dose reduction (as per TA529 assumption)
Myalgia	1	£162	Assumed to be same as arthralgia (Elizabeth Wehler *et al.* 2017)[68]
Neutropenia	-	-	Managed by dose reduction (as per TA529 assumption)

Pulmonary embolism	5	£1,411	NHS reference costs 2017/2018 weighted average of Pulmonary Embolus with Interventions-Total HRG activity: DZ09J-Q
Thrombocyte	2	£278	NHS reference costs 2017/18; Thrombocytopenia with CC Score 0-1 SA12K (day case)
Weight increased	-	-	Assumed to incur no costs (as per TA529 assumption)
Abbreviations: AEs, adverse events; CC, cubic centimetre; TA, technology appraisal.			

The unit costs were applied to the proportions of patients expected to experience each of the AEs for each treatment regimen (described in Section 5.3.6) and summed for each treatment group to generate an overall expected cost per patient. These overall costs per patient, as presented in Table 35, were applied as a one-off cost in the first model cycle.

Table 35. Total cost of adverse event management per patient

Treatment arm	One-off AEs costs
Entrectinib	£24.18
Crizotinib	£40.80
Pemetrexed plus platinum	£539.75
Abbreviations: AEs, adverse events.	

5.3.8.5 ROS1 testing costs

A key aspect of targeting treatment for patients with ROS1 genetic fusions is the requirement to test for these fusions to confirm eligibility for targeted treatment. As ROS1+ patients are only a small proportion of the total NSCLC population, this means there is a notable additional cost incurred by the increased numbers of patients who receive a test in the NSCLC population; a much larger group than just the ROS1+ patients.

To estimate the expected cost of the testing required to identify a patient who is ROS1+, the company estimated the prevalence of ROS1+ patients among non-squamous NSCLC patients. The assumptions used were in line with those in TA529, in which a value of 1.69% was used. This value was used to estimate the total number of patients who would be expected to be tested for ROS1 fusions.

The testing for ROS1 fusions is done in two stages with two different tests. The first test performed is an immunohistochemistry (IHC) test, which was assumed to have a sensitivity of 100% and a specificity of 83% as measured against the reference standard fluorescence *in situ* hybridisation (FISH) test. The FISH test was then used as a confirmatory test in the 1.69% of patients who were correctly identified as ROS1 and in the 17% of the non-ROS1+ patients who were assumed to be falsely identified with ROS1 genetic fusions. As the FISH test was the reference standard, it was assumed that this test is both 100% sensitive and 100% specific.

The IHC test was assumed to cost £50 and the FISH test £120, in line with the costs used in TA529. These costs were first weighted by the proportions expected to receive each in the overall population

non-squamous NSCLC, i.e. 100% for the IHC, and 1.69% plus 17% for the FISH test. These costs were then summed and scaled up by the reciprocal of the prevalence of ROS1+ patients to give a cost of £4,286 in tests for every patient identified with ROS1 genetic fusions. A summary of the calculations is given Table 36.

Table 36. ROS1 testing costs (adapted from Table 54, page 149 of the CS)

Test	Cost
IHC	£50
FISH	£120 IHC positive test: (1.69%+17%) =18.7% Cost of FISH testing £120*18.7% = £22.43
Expected cost per patient tested	£50+22.43= **£72.43**
Total cost per ROS1-positive patient diagnosed	£72.43/1.69% = **£4,285.68**
Key: FISH, fluorescence in situ hybridisation; IHC, Immunohistochemistry.	

5.3.8.6 Subsequent treatment costs

The company used data from the entrectinib clinical trials (STARTRK-1 and STARTRK -2) to estimate the proportion of patients expected to receive certain subsequent treatments after progression while receiving the primary treatment. These proportions were then adjusted to account for clinical expert opinion provided to the company. The latter consisted on: the proportion of patients receiving crizotinib would be zero following treatment with entrectinib in the comparison versus PEM+PLAT; the proportion receiving crizotinib would be zero following crizotinib primary therapy; and, the proportion receiving pemetrexed, carboplatin or cisplatin would be zero following treatment with pemetrexed plus platinum. The proportions of patients receiving each subsequent treatment in the model is given in Table 37. The dosing and unit costs of each of the drugs received as subsequent treatments are given in Table 38.

Table 37. Proportions of subsequent treatments assumed in the model (adapted from Table 55, page 150 of the CS)

Subsequent therapy	Entrectinib (base case versus pemetrexed plus platinum)	Entrectinib (key scenario analysis versus crizotinib)	Crizotinib	Pemetrexed plus platinum
Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]

Pemetrexed disodium	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]

Table 38. Subsequent treatment doses and unit costs (adapted from Table 56, page 151 of the CS)

Treatment	Dose	Frequency	Unit size (mg)	Unit cost	Source
Pemetrexed	500.00mg/m2	Day 1 of 21-day cycle (IV)	100	£159.67	MIMS
			500	£795.19	
Carboplatin	AUC 5–6 IV		50	£3.07	eMIT
			450	£17.03	
			600	£17.54	
			150	£6.65	
Cisplatin	75.00mg/m2		10	£1.53	eMIT
			50	£4.25	
			100	£9.26	
Nivolumab	3.00mg/Kg	Day 1 of 14-day cycle (IV)	40	£439.00	MIMS
			100	£1,097.00	
			240	£2,633.00	
Crizotinib	500.00mg	Daily (oral)	30 (250mg)	£4,689	MIMS
Docetaxel	75.00mg/m2	Day 1 of 21-day cycle (IV)	20	£5.75	eMIT
			80	£11.95	
			160	£30.82	
Gemcitabine	1000.00mg/m2	Day 1 and 8 of 21-day cycle (IV)	1,200	£32.21	eMIT
			1,600	£36.02	
			1,800	£38.82	
			2,000	£42.86	
			2,200	£44.98	
			200	£4.48	
Paclitaxel	200.00mg/m2	Day 1 of 21-day cycle (IV)	100	£9.49	eMIT
			150	£24.01	
			300	£25.26	
			30	£8.62	
Bevacizumab	11.25mg/Kg	Day 1 of 21-day cycle (IV)	100	£242.66	MIMS
			400	£924.40	
Erlotinib	150.00mg	Daily (oral)	30 (25mg)	£378.33	MIMS
			30 (100mg)	£1324.14	
			30 (150mg)	£1631.53	

Abbreviations: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialties.

Duration of subsequent treatments was largely derived from data in relevant NICE appraisals. Chemotherapy (carboplatin or cisplatin with pemetrexed, docetaxel, gemcitabine and paclitaxel) was assumed to have a duration of 3.3 months in line with TA428;[31] nivolumab and bevacizumab were assumed to have an average dose of 12.6 and 8.9 months, respectively, based on TA484[30] and Trial E4599; and, erlotinib was assumed to have an average duration of 11 months based on TA310.[69] Due

to a lack of ToT data, crizotinib was assumed to be given until progression, and the company used the median PFS in PROFILE 1001 of 19.22 months to estimate subsequent the cost of subsequent crizotinib.

The company multiplied these proportions by each of the respective costs to produce a weighted average cost of subsequent treatments for each patient. This cost was applied in the model as a one-off cost at the point of progression. The one-off costs for entrectinib (versus PEM+PLAT); PEM+PLAT; crizotinib, and entrectinib (versus crizotinib); are, £4,815; £3,541; £8,305; and, £4,815, respectively.

5.3.8.7 ERG critique

The ERG considers the company's approach to sourcing and applying unit costs and resource use in the economic model to be generally sound but notes a few areas where the modelling could have been improved or where uncertainties remain. In addition to this, some of the estimates of resource use included in the company's base case did not align with the clinical expert opinion received by the ERG.

The first of the key issues relates to the maintenance therapy assumed in the company's base case, for which there are two issues: the restriction of maintenance therapy to only patients who have received pemetrexed with cisplatin (therefore excluding patients who received pemetrexed with carboplatin); and, the assumption of a fixed number of 4 treatment-cycles post-progression.

These issues were highlighted by the clinical experts advising the ERG, who noted that current clinical practice has changed relatively recently and now pemetrexed maintenance therapy can be given after initial treatment with pemetrexed in combination with either cisplatin or carboplatin. The ERG, therefore, requested that the company provided an option in the economic model to allow for maintenance therapy to be included following both cisplatin and carboplatin.

With regard to the duration of maintenance therapy, the ERG's clinical experts suggested that maintenance therapy is generally given until progression of disease, for a maximum of 2 years or 20 cycles of treatment. Therefore, the ERG considers the company's approach (no maintenance treatment in the base case and 4 cycles as a scenario analysis) may underestimate the mean number of treatment cycles expected to be received for maintenance. The ERG considers that applying maintenance costs until progression (and for a maximum of 2 years) is a more accurate reflection of UK clinical practice. Results of this scenario analysis are reported in Section 6.

The ERG also notes that there should be an alignment with the treatment effectiveness estimates in terms of maintenance therapy when considering the application of these costs and that PROFILE 1014 did not include maintenance treatment with pemetrexed (whereas ASCEND-4 did as discussed in Section 5.3.5).[70] Therefore, even though the ERG reports a scenario analysis including maintenance costs until disease progression in the company's base case (using the ERG's preferred efficacy set) in

Section 6, caution is warranted when interpreting this scenario. The ERG also provides the same scenario for when treatment effectiveness for PEM+PLAT is estimated using ASCEND-4.

Another point relating to PEM+PLAT noted by the ERG's clinical experts is that the proportion of patients expected to receive either cisplatin or carboplatin as the platinum-based chemotherapy in the company's base case analysis is not reflective of current UK clinical practice. Clinical expert opinion suggested that, although cisplatin is considered the better option if it can be tolerated, generally more people receive carboplatin as it is easier to tolerate. The ERG's clinical experts suggested that around 80% of patients could be expected to receive carboplatin with the remainder receiving cisplatin. This is a sizable difference from the company's base case, which assumed 54% of patients received cisplatin and 46% of patients received carboplatin. The consequence of this change is only important under the company's assumption of maintenance only following cisplatin. However, under the assumption of maintenance therapy following either platinum regimen, the impact becomes minimal, with the expected per-cycle acquisition cost of pemetrexed plus platinum increasing by just £1 when it is assumed that 80% of patients receive carboplatin.

The next key issue relates to the company's apparently simplistic approach to applying subsequent treatment costs, and in particular the inaccurate accounting of discount factors to apply for subsequent treatments received beyond the model cycle in which the subsequent treatments commenced. The company calculated an expected per-patient cost of subsequent treatments that was multiplied by an estimate of the newly progressed patients in each model cycle, at which point a discount factor relating to that model cycle was applied. The ERG considers this approach to underestimate the discounting that should be applied to the later doses of subsequent treatments received as it effectively applies the smallest initial cycle discount factor, relevant to only the first dose, to each subsequent dose.

At the clarification stage, the ERG asked the company to use a more accurate approach to discount each dose appropriately. In response to clarification questions, the company provided an alternative approach in which a greater discount was applied to each model cycle in an attempt to capture the greater discount factors for subsequent treatments receive later. However, the ERG considers the alternative approach to be also inaccurate and now overestimates the impact of discounting by taking the discount rate for the model cycle at the end of subsequent treatment duration. The ERG considers the appropriate discount factor should be the moving average of the discount factors from model cycle in which subsequent treatments commence to the last expected model cycle in which subsequent treatments would be received for those patients. The ERG has corrected this and updated the company's corrected base case in Section 6.1.

The ERG was also concerned with the proportions of subsequent treatments applied by the company in the economic model. Firstly, the company only took data from the entrectinib trials (STARTRK-1 and

STARTRK-2) and applied these to the comparator treatment groups with some adjustments to account for clinically implausible combinations of treatments, e.g. no subsequent crizotinib following crizotinib. These data may not, therefore, reflect the treatments used in the trials that were used to inform the treatment effectiveness. Thus, there is a potential disconnect between the effects and costs applied, which could bias the cost effectiveness results. Further to this, these treatments do not fully reflect UK clinical practice, as most patients would be expected to receive PEM+PLAT after entrectinib or crizotinib. During clarification, the ERG has requested a scenario testing the impact of applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib. The results provided in Section 6.

The ERG is also concerned that the number of subsequent treatments received in the company's base case model is based on just [redacted] of the total number of patients. The ERG's clinical experts advised that approximately 100% of patients would be expected to receive subsequent treatments after progression. Further to this, this estimate is meant to include all lines of subsequent treatment and not just the second line. The total number of patients receiving subsequent treatments in the company's preferred efficacy set was [redacted], while in the ERG's efficacy set the proportion of patients receiving subsequent anti-cancer therapies was even less at [redacted]. The ERG is unclear why the proportion of patients receiving subsequent treatments is so low in the trials (when approximately 70% of patients had progressed in the ERG's preferred efficacy set).

The company did not respond to this issue when the ERG questioned why all progressed patients were not expected to receive subsequent treatments in the model as part of their response to clarification questions. The ERG explored the impact of scaling up the proportions of subsequent treatments applied in the company's base case so that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments, however this approach needs to be caveated by the fact that it illustrates a cost scenario disconnected with the underlying trial data (at least for entrectinib) and reports the results in Section 6. Subsequent treatments received in PROFILE 1001 were not reported by the company, and therefore, this remains an outstanding source of uncertainty in the model.

Furthermore, the ERG's clinical experts considered some of the company's assumption related to the resource use for disease management to not be fully reflective of UK clinical practice. Therefore, the ERG tested the impact of the clinical expert's suggested resource use in a scenario analysis. A comparison of the company's base case inputs with the ERG's clinical expert informed inputs is given in Table 39. The results of the scenario in which the ERG's clinical expert informed inputs are applied are given in Section 6.

Table 39. Comparison of company's and ERG's preferred disease management resource use

Resource required	Company's assumptions				ERG's clinical expert assumptions			
	PFS		PPS		PFS		PPS	
	% patients	Frequency per month	% patients	Frequency per month	% patients	Frequency per month	% patients	Frequency per month
Outpatient visit	100%	0.75	100%	1.00	100%	1.00	100%	1.00
GP visit	10%	1.00	28%	1.00	10%	0.33	28%	1.00
Cancer nurse	20%	1.00	10%	1.00	20%	0.33	50%	1.00
Complete blood count	100%	0.75	100%	1.00	100%	1.00	100%	1.00
Biochemistry	100%	0.75	100%	1.00	100%	1.00	100%	1.00
CT scan	30%	0.75	5%	0.75	100%	0.50	30%	0.75
Chest X-ray	30%	0.75	30%	0.75	0%	0.00	0%	0.00

A final minor issue was noted in relation to the estimation of testing costs expected to be incurred to identify a ROS1+ patient. To estimate the number of patients expected to incur the costs of the FISH test, the company summed the prevalence of the ROS1+ gene fusion of 1.69% with the false positive rate of 17%. However, the false positive rate is the proportion of patients who do not have the ROS1+ gene fusion who test positive. Therefore, this rate needs to be multiplied by the proportion of patients who are expected to have no ROS1+ gene fusions (100% - 1.69% = 98.31%). The proportion of patients expected to incur the FISH test costs after testing positive on the IHC test, is then 18.4%; slightly lower than the company's estimate of 18.7%. This results in the expected testing cost reducing from £4,286 to £4,265. This has been corrected by the ERG and is incorporated into the company's corrected base case in Section 6.1.

The cost of testing is dependent on estimates of the prevalence of the ROS1+ gene fusion being present as well as to the sensitivity and specific of the genetic test; both the IHC test and the FISH test used for confirmation in those tested positive with the IHC test. The ERG's clinical experts suggested that the prevalence may be less than 1%, which has an important impact on the estimated size of the population required to be tested to identify each ROS1+ patient and therefore could have an important impact on the resulting ICER. Therefore, the ERG conducted two scenario analysis assuming a prevalence of 1% and 0.5% to assess the impact of this parameter on the ICER and presents results in Section 6.

5.4 Results included in company's submission

5.4.1 Base case results based on the company's preferred analysis set

The company did not change its base case results after the clarification stage. The deterministic base case results for entrectinib compared with PEM+PLAT and crizotinib are provided in Table 40 and

Table 41, respectively, with entrectinib's patient access scheme (PAS) included. To note is that the life years gained reported in the CS are discounted life years. The ERG finds discounted life years to be meaningless, thus reported the undiscounted life years gained with the different treatments in the tables below.

Table 40. Company's base case results with PAS included for entrectinib vs PEM+PLAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,930	1.51	1.01	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,628

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 41. Company's base case results with PAS included for entrectinib vs crizotinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	137,637	4.35	2.63	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

5.4.2 Base case results based on the ERG's preferred efficacy set (without any ERG's corrections)

The deterministic base case results for entrectinib compared with PEM+PLAT and crizotinib using the ERG's preferred efficacy set and the company's preferred model assumptions are provided in Table 42Table 40 and Table 43, respectively, with entrectinib's PAS included. The life years reported in the tables are undiscounted. Using the ERG's preferred efficacy set (and the company's base case assumptions) increases the ICER for entrectinib vs PEM+PLAT from £15,628 to £21,057 per QALY gained, while the ICER for entrectinib vs crizotinib remains dominated. Nonetheless, there is an overall reduction of life-years gained (LYG) with all treatments in the ERG's preferred efficacy set. The difference is particularly noted for entrectinib, for which the total LYG and QALY gain in the company's preferred analysis set is [redacted] and [redacted], respectively, and in the ERG's preferred set decreases to [redacted] and [redacted], respectively.

Table 42. Company's base case results with PAS included for entrectinib vs PEM+PLAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,021	1.20	0.82	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,057

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 43. Company's base case results with PAS included for entrectinib vs crizotinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	£124,410	3.46	2.16	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

5.4.3 Sensitivity analysis using the company's preferred analysis set

The company's deterministic sensitivity analysis can be found in the CS (pages 171 to 178). In summary, the key model drivers identified by the company's one-way sensitivity analysis (OWSA) were the OS HR for entrectinib vs crizotinib, followed by the HR for crizotinib vs PEM+PLAT (which is directly influenced by the OS HR for entrectinib vs crizotinib). Other key drivers of the company's economic results are the PFS HR for entrectinib vs crizotinib and the utility values used for the PFS and the PPS states in the analysis.

5.4.3.1 Probabilistic sensitivity analysis

The company's PSA results (Table 44 and Table 45) are in line with the deterministic ones, with total costs and QALYs quite similar for both treatment comparisons in both analyses.

Table 44. Company's PSA results with PAS included for entrectinib vs PEM+PLAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,629	1.52	1.07	-	-	-	-
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 45. Company's PSA results with PAS included for entrectinib vs crizotinib

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	£138,957	3.93	2.73	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 31 represents the scatter plot of the incremental costs and QALYs from the company's PSA results based on 2,000 iterations. The cost-effectiveness acceptability curve - CEAC (Figure 32), shows that entrectinib has a 100% probability of being cost-effective versus PEM+PLAT considering the £50,000 willingness-to-pay (WTP) threshold.

Figure 31: Cost-effectiveness plane – entrectinib (with PAS) versus pemetrexed plus platinum (list price)- company's base case

Figure 32: CEAC – entrectinib (with PAS) versus pemetrexed plus platinum (list price) – company's base case

The conclusion of the company's PSA results for the comparison of entrectinib with crizotinib was that entrectinib always dominates crizotinib and is always cost-effective regardless of the WTP threshold, when considering the PAS discount for entrectinib and crizotinib at list price. Nonetheless, the ERG is concerned that the analysis based on the crizotinib's list price is meaningless, as crizotinib is currently available in the CDF with a confidential discount.

The company's PSA appears to be generally sound and the ERG has not identified any technical errors in its application. However, the ERG notes a few issues to highlight.

Firstly, the ERG notes that the company has included drug unit costs within the PSA, which are varied using an arbitrary standard error of 10% of the mean value. However, the ERG considers these values should be fixed in the PSA, as they are known values with no uncertainty. The ERG re-ran the PSA on the company's base case and generated an ICER of [redacted] per QALY for entrectinib compared to PEM+PLAT; very similar to the company's PSA result of [redacted] per QALY. This small difference may also be a result of sampling error, as the company did not apply a seed to replicate the results using the same random numbers.

In addition to this, the company has applied normal distributions for all cost estimates in the PSA, meaning that in theory, negative costs could be sampled. However, given that the company assumed arbitrary standard errors of 10%, the sampled values are stable and are unlikely to result in negative values. The ERG considers that the company could have derived more accurate estimates of the standard errors using the data provided in NHS reference costs, for example. The company's approach could be

underestimating the variation in costs, which could impact the results. Furthermore, the potential skew in cost data is lost by applying normal distributions, so the ERG considers that either a gamma or lognormal distribution may have been more suitable to model this skew, which is common with costs as they are bound by zero.

The company also applied potentially unsuitable distributions for the frequency of disease management resource use values, which were sampled using beta distributions. This means that these frequencies are restricted to a maximum of 1 per month. Given that it is theoretically possible to have more than one of each of the resource use items in any given month, the ERG considers that a distribution that has no upper bound may be more suitable. However, in practice, the ERG considers it unlikely for plausible values to go far beyond 1, if at all. Therefore, the ERG does not consider this an important issue.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG described the errors found in the company's analysis throughout Section 5 of this report. These are summarised here, together with the combined impact of the corrections on the final ICER. The ERG presents the company's base case analysis set, together with the ERG's preferred efficacy set results. The ERG made the following corrections:

1. The ERG asked the company to change the half-cycle correction so that the first cycle of the model began with 100% of patients receiving the initial treatment dose. The company has provided this as a scenario analysis, instead of incorporating the change in their base case analysis. However, the ERG considers this to be an implementation mistake in the model, and therefore used the company's model switch to change the half-cycle correction as requested;

2. The ERG asked the company to apply discount factors that accounted for the later doses of subsequent treatments received (instead of applying subsequent treatment costs as a one-off cost for all newly progressed patients). The company has provided this as a scenario analysis, however the ERG disagrees with the company's approach and therefore implemented its own correction. The company's approach effectively applies the discount rate associated with the time at the end of the assumed subsequent treatment period. However, the ERG's preferred approach is to use the moving average of discount rates from the time at which the subsequent treatments commence until the time at which they are assumed to discontinue;

3. The ERG identified a minor error in company's calculation of the expected cost of ROS1 gene fusion testing, as one minus the specificity of the ICH test was assumed to be the proportion of patients with a false positive diagnosis. However, this should have been multiplied by the proportion of patients without the ROS1 gene fusion; i.e., one minus the prevalence. As the prevalence was very low, this had only a small impact on the results;

4. The ERG noted a final error regarding the application of HRG costs for the management of AEs. The company multiplied the total HRG costs for each AE by an assumed number of days that the patient would be expected to spend in hospital. However, the HRG costs represents a total cost of care, inclusive of inpatient stay. The company's assumption that these are daily costs is incorrect, so the ERG has removed the multiplication by hospital days and applied the HRG as a single cost for each AE.

Table 46 and Table 47 report the impact of the corrections on the company's preferred analysis set, while Table 48 and Table 49 report the same for the ERG's preferred efficacy set, for the comparison

of entrectinib vs PEM+PLAT and crizotinib, respectively. Overall, the corrections led to a relatively small increase in the ICER for entrectinib vs PEM+PLAT, while crizotinib remained dominated.

Table 46. Company's base case results with PAS included for entrectinib vs PEM+PLAT (with corrections)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£21,313	1.59	1.07	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,139
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.							

Table 47. Company's base case results with PAS included for entrectinib vs crizotinib (with corrections)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	£142,112	4.43	2.68	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.							

Table 48. Company's base case results with PAS included for entrectinib vs PEM+PLAT (with corrections) for ERG's preffered analysis set

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,470	1.28	0.87	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,845
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.							

Table 49. Company's base case results with PAS included for entrectinib vs crizotinib (with corrections) for ERG's preffered analysis set

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	128,926	3.54	2.22	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.							

6.2 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. Some of the analyses were requested during the clarification stage, however, given the company did not

change its base case results after the clarification process, the ERG presents these changes to the model in this section. The exploratory analyses presented by the ERG are based on the ERG's preferred efficacy set for entrectinib and the updated PROFILE 1001 data (as explained in Section 5) and Table 50 reports results for entrectinib vs PEM+PLAT while Table 51 reports results for entrectinib vs crizotinib. The analyses consist on the following:

12. The ERG ran a scenario analysis to assess the impact of using a Weibull distribution to fit PFS data for entrectinib in the model;

13. The ERG ran a scenario analysis using a Weibull curve to fit ToT in the economic model;

14. The ERG conducted sensitivity analysis assuming a PFS HR=1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression;

15. The ERG conducted sensitivity analysis assuming an OS HR=1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in extending life;

16. The ERG ran a scenario analysis using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS;

17. The ERG assumed that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments (however this approach needs to be caveated by the fact that it illustrates a cost scenario disconnected with the underlying trial data at least for entrectinib);

18. The ERG tested the impact of the clinical expert's suggested resource for the PFS and PPS health states;

19. The ERG has tested the impact of applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib (a scenario analysis provided by the company during clarification);

20. The ERG conducted assessed the impact changing the prevalence of ROS1+ from 1.69% to:

    a. 1%;

    b. 0.5%;

21. Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using:

a. The company's base case effectiveness assumption for PEM+PLAT (estimated with the PROFILE 1014 HR);

b. The alternative effectiveness assumption for PEM+PLAT (estimated with the ASCEND-4 MAIC);

22. Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT. To note is that this scenario also changes the duration of treatment with PEM+PLAT from 6 to 4 cycles in the model, to match the duration of treatment with PEM+PLAT in ASCEND-4.

Results from the ERG's scenario analysis show that for the comparison of entrectinib with PEM+PLAT the key model driver is the source of effectiveness chosen to estimate OS and PFS for PEM+PLAT, with the ICER increasing from £21,845 to £52,399 per QALY gained when treatment effectiveness is estimated with the ASCEND-4 MAIC HR instead of the PROFILE 1014 HR. This increase is due to a much smaller survival gain relative to entrectinib estimated with the ASCEND-4 data than with PROFILE 1014. Equally important in driving the model results is the assumption around the duration of maintenance treatment with pemetrexed, as it considerably increases treatment costs for the comparator in the company's base case assumptions. However, when combined with the scenario analysis assuming that all entrectinib patients receive PEM+PLAT as a subsequent treatment, the impact of the duration of maintenance treatment on the ICER is reduced. To note is that the company assumed a maximum treatment duration of 8 months for maintenance treatment with pemetrexed when given as a subsequent treatment.

As the prevalence of ROS1+ decreases, the cost for identifying a true-positive patient increases. However, the ERG notes that in the comparison of entrectinib with crizotinib, these costs cancel out as patients assigned to first-line treatment would have to be tested regardless of receiving one treatment or the other. For the comparison of entrectinib vs PEM+PLAT, the ERG finds the inclusion of ROS1+ fusion testing somewhat meaningless as this is a relevant treatment comparison only for second-line treatment, at which point this test would have already occurred.

Using the raw mean utilities from STARTRK-2 ([redacted] for PFS and [redacted] for PPS) decreases the ICER from £21,845 to £19,940 as the QALY loss associated with progressing increases (i.e. the difference in values is bigger) compared to the company's base case estimates.

Finally, it should be noted that assumptions around the ToT for entrectinib and the OS HR for entrectinib vs crizotinib also drive the PEM+PLAT comparison results. This is because the PEM+PLAT OS and PFS curves are estimated (in the company's base case approach) by applying the PROFILE 1014 HR to the crizotinib OS and PFS curves, respectively.

All the scenario analyses undertaken for the comparison of entrectinib with crizotinib produced dominant ICERs for entrectinib, with the exception of assuming no survival benefit between entrectinib and crizotinib. In the latter scenario the ICER amounts to £3,341,867 per QALY gained for crizotinib vs entrectinib, as the company's PFS MAIC resulted in favourable results for crizotinib (i.e. patients progress faster on entrectinib than on crizotinib). Thus, if no survival gain is assumed to "compensate" for the negative PFS impact, patients accrue less QALYs on entrectinib than on crizotinib albeit at a lower cost. Nonetheless, the ERG reiterates its concerns that the analysis based on the crizotinib's list price is meaningless, as crizotinib is currently available in the CDF with a confidential discount.

Table 50. Results of the ERG's scenario analysis for entrectinib vs PEM+PLAT

Analysis from list	Results per patient	Entrectinib (1)	PEM+PLAT (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,845**	
1	**Using a Weibull distribution to fit PFS**			
	Total costs (£)	[redacted]	20,422	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,835**	
2	**Using a Weibull distribution to fit ToT data for entrectinib in the model**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£24,366**	
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	20,464	[redacted]
	QALYs	[redacted]	0.86	[redacted]
	ICER		**£21,736**	
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	21,507	[redacted]
	QALYs	[redacted]	1.10	[redacted]
	ICER		**£24,216**	
5	**Using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.96	[redacted]
	ICER		**£19,940**	
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	21,662	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,796**	
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS sates**			

	Total costs (£)	[redacted]	21,299	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£22,812**	
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£22,530**	
9a	**Changing the prevalence of ROS1+ from 1.69% to 1%;**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£23,380**	
9b	**Changing the prevalence of ROS1+ from 1.69% to 0.5%;**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£27,142**	
10a	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using the company's base case effectiveness assumption for PEM+PLAT (estimated with the PROFILE 1014 HR)**			
	Total costs (£)	[redacted]	35,801	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£13,653**	
10b	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years) using the company's base case effectiveness assumption for PEM+PLAT (estimated with the ASCEND-4 MAIC)**			
	Total costs (£)	[redacted]	39,889	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER		**£27,940**	
11	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of treatment with PEM+PLAT from 6 to 4 cycles to match the duration of treatment with PEM+PLAT in ASCEND-4**			
	Total costs (£)	[redacted]	21,095	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER		**£52,399**	

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Table 51. Results of the ERG's scenario analysis for entrectinib vs crizotinib

Analysis from list	Results per patient	Entrectinib (1)	crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER		**Entrectinib is dominant**	
1	**Using a Weibull distribution to fit PFS data for entrectinib in the model**			
	Total costs (£)	[redacted]	131,011	[redacted]
	QALYs	[redacted]	2.22	[redacted]

	ICER	**Entrectinib is dominant**		
2	**Using a Weibull distribution to fit ToT data for entrectinib in the model**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	112,864	[redacted]
	QALYs	[redacted]	2.20	[redacted]
	ICER	**Entrectinib is dominant**		
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	131,065	[redacted]
	QALYs	[redacted]	2.77	[redacted]
	ICER	**£3,341,867**		
5	**Using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS**			
	Total costs (£)	[redacted]	128,926	[redacted]
	QALYs	[redacted]	2.43	[redacted]
	ICER	**Entrectinib is dominant**		
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	129,560	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS states**			
	Total costs (£)	[redacted]	131,040	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	129,665	[redacted]
	QALYs	[redacted]	2.22	[redacted]
	ICER	**Entrectinib is dominant**		

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

6.3 ERG base case ICER

The assumptions incorporated in the ICERs presented in Table 52 (entrectinib vs PEM+PLAT) include the cumulative impact of some of the scenario analyses numbered and described in Section 6.2. The ERG caveats the analyses presented with the high degree of uncertainty embedded in the MAICs undertaken to generate relative treatment effectiveness estimates in the model and the single-arm, immature STARTTRK-2 data available for entrectinib.

In order to reflect the lack of statistical significance in the OS and PFS results in the MAIC comparing entrectinib with crizotinib, and to address the problem related with the disconnected PFS "loss" of [redacted] months for entrectinib patients compared to crizotinib patients and the PPS gain of [redacted] months for entrectinib, the ERG assumed a PFS HR=1 and a OS HR =1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression and extending life. This is line with the conclusions reached in TA422, where an FDA analysis was referenced which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib), suggesting that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence. Furthermore, assuming a PFS HR=1 for entrectinib vs crizotinib also helps mitigate the uncertainty around the differences in the ToT curve for entrectinib and crizotinib, as explained in Section 5.3.5.7.

The ERG used the utility values accepted in TA529 (PFS=0.81; PPS=0.66), as it considers the company's base case approach flawed and the unadjusted raw data less robust than the data previously accepted by the committee at TA529.

The ERG assumed that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments (however this approach needs to be caveated by the fact that it illustrates a cost scenario disconnected with the underlying trial data at least for entrectinib) and that all patients who progress on entrectinib or crizotinib receive PEM+PLAT as a subsequent treatment. The ERG also used the clinical expert's suggested resource for the PFS and PPS health states and assumed maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years).

Finally, the ERG used the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT, as it produced more conservative and clinically plausible survival gains compared with the company's base case approach, as explained in Section 5.3.

Table 52 shows the impact of combining the different scenarios. The final cumulative ICER for entrectinib vs PEM+PLAT amounts to £22,821 per QALY gained. However, this ICER is highly dependent on the assumption made for duration of maintenance treatment with pemetrexed. The ERG's base case ICER drops from £45,629 to £22,821, when it is assumed that maintenance treatment is given until progression. If, for example, maintenance treatment is assumed to be given for 6 cycles (as the clinical experts indicated to the ERG that this is a clinically plausible median duration), the ERG's ICER is £35,975 per QALY gained.

In ASCEND-4, maintenance treatment with pemetrexed was given every 21-days, until disease progression. Median PFS in ASCEND-4 was 8.1 months (mean not available in the publication), which amounts to 12 cycles of 21-days treatment cycles. Given that patients received 4 initial cycles of

PEM+PLAT, that leaves 8 cycles of maintenance treatment with pemetrexed. Assuming 8 cycles of maintenance treatment in the ERG's base case model results in a £34,000 per QALYs gained. The ERG notes that this ICER corresponds with aligning the treatment effectiveness of PEM+PLAT in the ERG's base case with the respective costs in the underlying ASCEND-4 study.

The ERG ran PSA for its preferred ICER for entrectinib vs PEM+PLAT. The resulting ICER (Table 53) amounts to £25,262 per QALY gained.

Given the ERG's assumption of equal effectiveness for entrectinib and crizotinib in terms of progression and survival, presenting an ICER comparing these treatments was no longer meaningful as the QALY gain in the analysis is zero. The only scenarios relevant in this comparison (i.e. affecting the costs of either entrectinib or crizotinib) were therefore: assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments; and that all patients who progress on entrectinib or crizotinib receive PEM+PLAT as a subsequent treatment.

The total crizotinib costs in the ERG's preferred analysis amounts to £118,912, while the total costs for entrectinib amounts to [redacted]. With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (i.e. [redacted]). If the total costs associated with crizotinib were lower than [redacted] then the ICER for entrectinib vs crizotinib would increase as the cost for crizotinib decrease.

Table 52. ERG's base case ICERs for entrectinib vs PEM+PLAT

Analysis from list	Results per patient	Entrectinib (1)	PEM+PLAT (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,845**	
3	**Assuming a PFS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	20,464	[redacted]
	QALYs	[redacted]	0.86	[redacted]
	ICER with all changes incorporated		**£21,736**	
4	**Assuming an OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	21,493	[redacted]
	QALYs	[redacted]	1.09	[redacted]
	ICER with all changes incorporated		**£24,083**	
-	**Using the TA529-accepted utility values of of 0.81 for PFS and 0.66 for PPS**			
	Total costs (£)	[redacted]	21,493	[redacted]
	QALYs	[redacted]	1.15	[redacted]

	ICER with all changes incorporated	**£23,172**		
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	24,388	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£22,130**		
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS sates**			
	Total costs (£)	[redacted]	25,431	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£23,058**		
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	25,431	[redacted]
	QALYs	[redacted]	1.15	[redacted]
	ICER with all changes incorporated	**£23,164**		
11	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of treatment with PEM+PLAT from 6 to 4 cycles to match the duration of treatment with PEM+PLAT in ASCEND-4**			
	Total costs (£)	[redacted]	27,682	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER with all changes incorporated	**£45,629**		
10b	**Assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years)**			
	Total costs (£)	[redacted]	46,475	[redacted]
	QALYs	[redacted]	2.05	[redacted]
	ICER	**£22,821**		

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Table 53. ERG's PSA results with PAS included for entrectinib vs PEM+PLAT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	45,227	2.96	2.09	-	-	-	-
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,262

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

7 END OF LIFE

The company provided evidence to support the consideration of entrectinib as an end of life treatment for locally advanced or metastatic ROS1-fusion positive advanced non-small-cell lung cancer (ROS1+ NSCLC). The company's rationale for the criteria outlined by the National Institute for Health and Care Excellence (NICE) are presented in Table 54 with a comment from the Evidence Review Group (ERG).

The ERG considers the evidence presented by the company regarding life expectancy of less than 24 months to be inconsistent with results for OS with crizotinib and PEM+PLAT in the ERG's base case model and for crizotinib in the company's model. The mean OS for crizotinib in the company's model (4.35 years) and in the ERG's model (4.62 years) suggest that patients, on average, will live for longer than 24 months on this treatment. The same is true for PEM+PLAT in the ERG's model (3.22 years in the ERG's base case analysis). The company's base case estimates that survival with PEM+PLAT is 1.51 years.

The inconsistency in the company's argument for crizotinib implies that either the model (both the company's and the ERG's) is overestimating survival with crizotinib and, thus potentially also with entrectinib; or that entrectinib does not fulfil the first criteria for being considered an end of life treatment.

With regard to the second criterion, the company's base case suggests a substantial extension to life which is incongruous with PFS being shorter with entrectinib than crizotinib. The ERG's considers there to be important limitations with the MAICs as highlighted in previous sections, and with the long-term extrapolation of OS based on immature data, and therefore does not consider there to be reliable evidence for a three-month extension to life with entrectinib compared with current NHS treatment.

Table 54. End of life considerations (adapted from CS, Table 34)

NICE criterion	Data highlighted by the company	Reference to submission	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS in patients with ROS1-positive NSCLC not treated with ROS1-targeted treatment in Korean clinical practice was 20.0 months.[13]	Section B.1.3, pg. 13	The mean OS for crizotinib in the company's model (4.35 years) and in the ERG's model (4.62 years) suggest that patients, on average, will live for longer than 24 months. The same is true for PEM+PLAT (1.51 years in the company's base case model and 3.22 years in the ERG's base case analysis).
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed-based chemotherapy in clinical trials ranges from 19.2 to 27.7 months across treatment settings (first- to third-line plus) but it should be noted that some patients went onto receive ROS1-targeted treatment post progression.[50, 70-73]	Appendix D.6, pg. 92	
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed plus platinum with pemetrexed maintenance in the first-line setting was 26.2 months in ASCEND-4 but this was not adjusted for crossover (43%	Section B.2.9, pg. 67	

	of patients switched to ROS1-targeted treatment post progression).[70]		
	Median OS in patients with ALK-positive NSCLC who did not receive crizotinib in PROFILE 1001 was 20.0 months.	Shaw et al. 2011	
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in the entrectinib integrated analysis, with only [redacted]% of patients having died at the time of the latest analysis ([redacted]) when the minimum follow-up was [redacted] months (median follow-up [redacted] months).[74, 75]	Section B.2.6, pg. 44	The ERG does not consider there to be sufficient evidence that entrectinib offers at least a 3-month extension to life compared with crizotinib, which is the standard treatment in the NHS. The ERG considers the company's modelled OS benefit of entrectinib highly uncertain due to the immaturity of OS and the lack of PFS benefit versus crizotinib.
	Median OS associated with crizotinib was 51.4 months in PROFILE 1001. KM plots of OS in MAIC estimate a survival advantage in favour of entrectinib versus crizotinib.[46]	Section B.2.9, pg. 59	
	Estimated LYG with entrectinib versus pemetrexed plus platinum with pemetrexed maintenance in the economic modelling is 4.49 years (base case).	Section B.3.7, pg 164	
Abbreviations: KM, Kaplan Meier; LYG, life years gained; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.			

8 OVERALL CONCLUSIONS

Clinical

The level of evidence available to assess the safety and efficacy of entrectinib against the relevant comparators for patients with ROS1 fusion-positive locally advanced or metastatic NSCLC (ROS1+ NSCLC) reflects the rarity of the condition. Evidence for entrectinib is limited to three ongoing, open-label, single-arm, mixed population studies which have so far enrolled [redacted] patients with ROS1+ NSCLC, and a much smaller number were included in the company's primary efficacy analyses (n = 53). Evidence for crizotinib in ROS1+ NSCLC – which the ERG agrees is the most relevant comparator despite only being available through the Cancer Drugs Fund (CDF) – is also limited to a single-arm study and observational data, and there are no directly relevant data for pemetrexed plus platinum therapy (PEM+PLAT). The ERG therefore highlights that results of all analyses are therefore associated with substantial uncertainty, but the ERG's preferred clinical effectiveness analyses differ from those of the company with regard to:

- the underlying efficacy set used for entrectinib;
- the maturity of data from PROFILE 1001 used for the MAIC between entrectinib and crizotinib;
- the preferred study and method to derive estimates for PEM+PLAT in the economic model.

The ERG considers the company's preference to exclude [redacted] patients from the primary efficacy set on the basis of follow-up duration inappropriate given the small number of patients with ROS1+ NSCLC that met the other criteria for analysis (n = 53). The ERG instead considers efficacy results based on the 78 patients from STARTRK-2 who all received the recommended starting dose of entrectinib, irrespective of follow-up, more appropriate for decision-making. STARTRK-2 is the only Phase II study of entrectinib and the only study designed to assess efficacy outcomes; it was also the only study to assess tumour scans prospectively which may mean results for ORR and PFS are less biased. Patients included in the ERG's preferred efficacy analyses with shorter follow-up contribute data for the efficacy outcomes reflected in the economic model (OS and PFS) up to the point at which they are censored, although OS is immature and unreliable regardless of the efficacy set chosen.

Efficacy results are generally [redacted] to entrectinib in the evidence review group's (ERG's) preferred analyses than those submitted by the company. Compared with the company's preferred analysis, the ERG's efficacy set showed [redacted] ORR ([redacted] vs [redacted]), [redacted] median DoR ([redacted] months vs [redacted] months), and [redacted] median PFS ([redacted] vs [redacted] months). OS was immature in both analyses and estimates are likely to be unreliable. The ERG considers crizotinib the most relevant comparator, and the ERG's preferred MAIC using PROFILE 1001 suggests a [redacted] OS benefit of

entrectinib compared with crizotinib than the MAIC using the company's preferences. The ERG's results also show different effects to the company's for ORR and PFS, with the ERG's preferred MAIC suggesting [redacted] in ORR between the treatments and a possible [redacted] of crizotinib over entrectinib for PFS [redacted].

The OS KM curves for comparing entrectinib and crizotinib are likely to be unreliable from approximately 20 months due to the level of censoring required ([redacted] and 69.8% for entrectinib and crizotinib in the company's MAIC and [redacted] and 49.1% in the ERG's preferred MAIC using updated results for PROFILE 1001), which introduces substantial uncertainty in the extrapolation required for the economic model. Moreover, OS observed in studies of ROS1+ NSCLC, including those used for the MAICs, is much longer than has been achieved in clinical practice (51.4 months for crizotinib in PROFILE 1001 versus 18.5 months in the Flatiron registry), so the results may not reflect the effectiveness that might be expected for patients treated in the NHS.

No evidence for PEM+PLAT is available in a population with ROS1+ NSCLC and considers there to be important limitations of both methods used to derive estimates for PEM+PLAT using evidence for ALK+ NSCLC. The ASCEND-4 MAIC is limited by the use of a proxy ALK+ NSCLC population, differences in prior treatment between the studies (all patients in ASCEND-4 were treatment-naïve), and treatment crossover from PEM+PLAT to crizotinib in ASCEND-4 which would not happen in UK practice. The ERG considers there to be no consensus about the appropriateness of using evidence from ALK+ NSCLC as a proxy for ROS1+ NSCLC, and there is no way to quantify or adjust for differences in absolute or relative treatment effects that are attributable to the underlying gene fusion. Results for the ERG's preferred MAIC using ASCEND-4 to derive estimates for MAIC, which was the ERG's preferred method, all lay in favour of entrectinib in line with the company's preferred results, but effects were generally [redacted] than the company's preferred MAIC.

Results from the alternative method of deriving estimates for PEM+PLAT using relative effects from PROFILE 1014 likely overestimate the benefit of entrectinib because the company use crossover-adjusted OS based on a method which was deemed flawed by the appraisal committee for TA529. Unadjusted results were considered preferable for TA529 because only 19% of patients had crossed over, but 84% had done so at the latest follow-up so this is no longer be reasonable. Furthermore, the hazard ratio for PFS from PROFILE 1014 is not reliable because the assumption of proportional hazards does not hold.[12] The ERG agreed that the PROFILE 1014 method retains the benefits of a randomised comparison and only assumes that the *relative* effect of crizotinib versus PEM+PLAT is similar for ALK+ and ROS1+ NSCLC but considers the limitations more serious than those of the ASCEND-4 MAIC, and the results were not clinically plausible.

The ERG notes that safety results for entrectinib presented with the clinical results are based on a different population to the efficacy results, because it was deemed appropriate to assess safety from a wider group of patients. It was only practical to consider overall discontinuation due to AEs in the MAICs, and so the adverse event profile of entrectinib relative to crizotinib and PEM+PLAT in the economic model is based on naïve comparisons from the associated studies.

Economic

The ERG's main concerns are related to the immaturity of OS data in the single-arm STARTRK-2 study, and the results of both the OS and PFS MAICs comparing entrectinib with crizotinib, which have shown non-statistically significant results. The ERG is concerned that survival with entrectinib is considerably overestimated in the economic analysis (using the ERG's preferred data set and even more so with the company's data set) and with the disconnected PFS "loss" of [redacted] months for entrectinib compared to crizotinib, and the PPS gain of [redacted] months associated with entrectinib (ERG's preferred efficacy set). The ERG has not heard from clinical experts that the PFS results favouring crizotinib vs entrectinib are expected in clinical practice, and so these could potentially be attributable to the inaccuracy of the MAIC results due to low statistical power or unadjusted for confounding factors.

Given the paramount uncertainty around the survival benefit for entrectinib compared with crizotinib, the ERG considered the most conservative approach to be one based on the advice given in TA422, which in its turn was based on the analysis by the FDA, which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib), suggesting that it is not unreasonable to assume similarity between PFS and OS treatment effects (in terms of additional months spent in these states) in the absence of other evidence. Therefore, the ERG's base case analysis assumes a PFS HR=1 and an OS HR =1 for entrectinib vs crizotinib, indicating that the drugs have a similar effect in delaying progression and extending life. The total crizotinib costs in the ERG's preferred analysis amount to £118,912, while the total costs for entrectinib amount to [redacted]. With this difference in total costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total costs in the economic analysis as entrectinib (i.e. [redacted]). If the total costs associated with crizotinib were lower than [redacted] then the ICER for entrectinib vs crizotinib would increase as the total costs for crizotinib decrease.

Overall, in light of the weak and uncertain evidence underpinning the relative treatment effect of entrectinib compared with crizotinib, the ERG is concerned with the fact that entrectinib, if recommended, is likely to displace crizotinib as a first-line treatment for ROS1+ NSCLC and that clinicians are unlikely to give second-line crizotinib after patients had received entrectinib.

Regarding the analysis of entrectinib vs PEM+PLAT, the ERG's concerns related to the uncertainty in the entrectinib data remain, however, there seems to be a more plausible relationship between PFS and OS outcomes for entrectinib vs PEM+PLAT, particularly when the ASCEND-4 MAIC results are used to estimate survival with PEM+PLAT (instead of the company's base case approach using PROFILE 1014). Entrectinib shows a statistically significant advantage over PEM+PLAT in delaying patients' disease progression and a non-significant, albeit positive trend, in OS.

The two approaches presented by the company to estimate OS for PEM+PLAT have considerable flaws. Nonetheless, given the conclusions in TA529 that the maximum expected survival benefit of crizotinib vs PEM+PLAT would be between 13 and 16 months; and the model results (where using the PROFILE 1014 HR in the ERG's preferred efficacy set yields a survival benefit of 27.5 months for crizotinib and using the ASCEND-4 MAIC HR produces a survival benefit of 3.9 months), the ERG considers that using the ASCEND-4 MAIC produces more conservative results.

A key driver of the economic results for entrectinib vs PEM+PLAT is the assumption made for duration of maintenance treatment with pemetrexed. The ERG's base case ICER drops from £45,629 to £22,821 when it is assumed that maintenance treatment is given until progression (mean time to progression is 11.43 months in the ERG's base case). If, for example, maintenance treatment is assumed to be given for 6 cycles (as the clinical experts indicated to the ERG that this is a plausible median duration), the ERG's ICER increases to £35,975 per QALY gained. Therefore, the ERG notes the importance of considering the clinical plausibility of this parameter.

8.1 Implications for research

The rarity of ROS1+ NSCLC means that study eligibility criteria need to be broad in terms of disease characteristics and prior treatments in order to recruit a sufficient number of patients, which poses challenges when assessing the applicability of the evidence for a narrower group of patients in a particular setting (e.g. those who are untreated in the UK). The best available evidence for entrectinib and crizotinib for ROS1+ NSCLC is from small single-arm studies, which can only be compared via an unanchored indirect comparison. More mature data from STARTRK-2 and PROFILE 1001 may help to resolve the current uncertainty regarding OS with entrectinib compared with crizotinib. [redacted].

No data comparing entrectinib with PEM+PLAT in a ROS1+ NSCLC population is likely to emerge because it would be unethical to withhold a more effective TKI treatment from patients, and so assumptions based on existing data from RCTs of ALK+ NSCLC are likely to remain the best available

option. As additional study results emerge for treatments in ROS1+ and ALK+ patients, a more robust estimate for the difference in treatment effect in these different mutations may become known.

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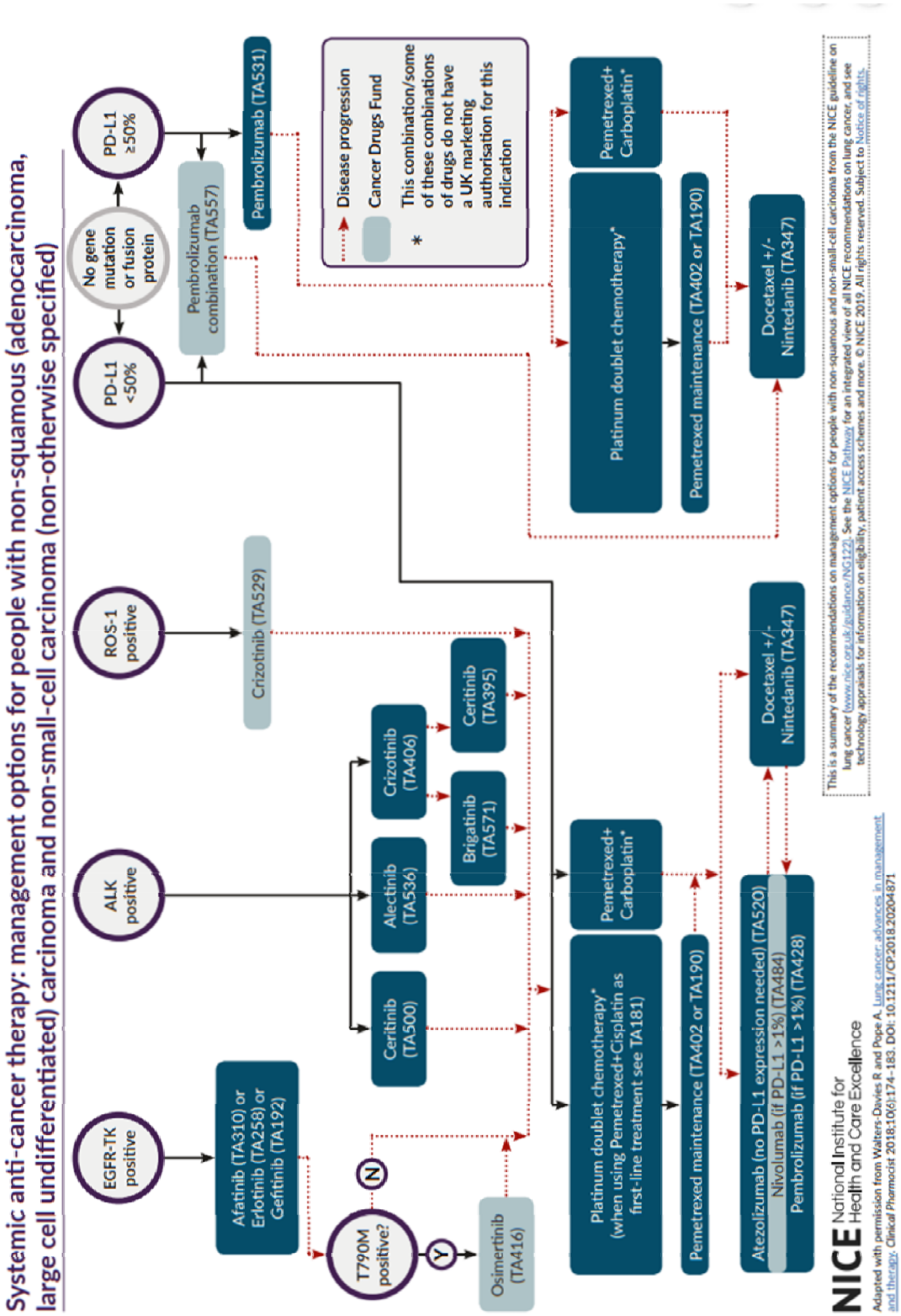
10 APPENDICES

10.1 Treatment pathway

Figure 33. NICE-recommended systemic anti-cancer therapies for non-squamous NSCLC, including non-squamous ROS1+ NSCLC[76]



10.2 Baseline characteristics

Table 55. Baseline characteristics for entrectinib and studies used for the indirect treatment comparisons (company and ERG preferred efficacy sets (adapted from CS, Table 5 and 17 and CQ response Table 9)

	Entrectinib		**Crizotinib**	**PEM+PLAT**
	Company efficacy set (n = 53)	**ERG efficacy set (n = 78)**	**PROFILE 1001 (n = 53)**	**ASCEND-4 (n = 187)**
Mean age (SD), years	53.5	53.3	NR	NR
Median age (range), years	53.0 (46.0, 61.0)	53 (28, 86)	55.0 (25.0, 81.0)	54.0 (22.0, 80.0)
Age categories (years), n (%)				
<65	42 (79.2)	62 (79.5)	NR	NR
≥65	11 (20.8)	16 (20.5)	NR	NR
Sex, n (%)				
Male	19 (35.8)	29 (37.2)	23 (43.4)	73 (39.0)
Female	34 (64.2)	49 (62.8)	23 (43.4)	73 (39.0)
Race, n (%)				
White	31 (58.5)	35 (44.9)	NR	NR
Asian	19 (35.8)	36 (46.2)	21 (39.6)	105 (56.0)
Black or African American	3 (5.7)	5 (6.4	NR	NR
ECOG Score, n (%)				
0	20 (37.7)	30 (38.5)	52 (98.1)	175 (94.0)
1	27 (50.9)	38 (48.7)		
2	6 (11.3)	10 (12.8)	1 (1.9)	11 (6.0)
No history of smoking, n (%)	31 (58.5)	44 (56.4)	40 (75.5)	122 (65.0)
Histology, n (%)				
Adenocarcinoma	35 (76.1)	76 (97.4)	51 (96.2)	183 (93.0)
Bronchioloalveolar carcinoma	1 (2.2)	1 (1.3)	NR	NR
Cytological	2 (4.3)	0	NR	NR
Histological	7 (15.2)	0	NR	NR
Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements	1 (2.2)	1 (1.3)	NR	NR
Time since diagnosis (months)				
Mean	21.0	20.7	NR	NR
Median (range)	11.5 (3.3, 28.9)	7 (0.7, 200.4)	NR	NR
Stage at initial diagnosis, n (%)				
IIIB	3 (5.7)	4 (5.1)	NR	5 (2.7)
IV (non-CNS)	4 (7.5)	22 (28.2)	NR	120 (64.1)
IV (CNS)	23 (43.4)	35 (44.9)	NR	62 (33.2)
Extent of disease, n (%)				
Localised	1 (1.9)	0	NR	NR
Locally advanced	2 (3.8)	1 (1.3)	NR	NR
Metastatic disease	50 (94.3)	77 (98.7)	NR	NR
Metastatic sites,[a] n (%)				
Bone	20 (37.7)	33 (42.3%)	NR	NR

Brain	23 (43.4)	35 (44.9%)	NR	NR
Liver	8 (15.1)	18 (23.1%)	NR	NR
Lung	38 (71.7)	39 (50%)	NR	NR
Lymph nodes	38 (71.7)	60 (76.9%)	NR	NR
Other	16 (30.2)	25 (32.1%)	NR	NR
Baseline CNS lesions by investigator,[b] n (%)				
Measurable	5 (9.4)	8 (10.3%)	NR	NR
Present	18 (34.0)	27 (34.6%)	NR	NR
Absent	30 (56.6)	43 (55.1%)	NR	NR
Prior treatments, n (%)				
Any prior therapy, n (%)	46 (86.8)	NR	NR	NR
Any prior systemic therapy	36 (67.9)	57 (73.1%)	NR	NR
Any chemotherapy	42 (79.2)	54 (69.2%)	NR	NR
Any immunotherapy	5 (9.4)	13 (16.7%)	NR	NR
Any targeted therapy	9 (17.0)	10 (12.8%)	NR	NR
Any hormonal therapy	1 (1.9)	1 (1.3%)	NR	NR
Prior radiotherapy of the brain	15 (28.3)	NR	NR	NR
Stereotactic Radiotherapy	3 (5.7)	NR	NR	NR
Whole Brain +/- Stereotactic Radiotherapy	5 (9.4)	NR	NR	NR
Any previous radiotherapy, n (%)	24 (45.3)	NR	NR	NR
Any previous surgeries, n (%)	27 (50.9)	NR	NR	NR
Number of prior systemic therapies,[c] n (%)				
0	17 (32.1)	31 (39.7%)	7 (13.2)	9 (5.0)
1	23 (43.4)	30 (38.5%)	20 (37.7)	NR
2	5 (9.4)	8 (10.3%)	13 (24.5)	NR
≥3	8 (15.1)	9 (11.5%)	13 (24.6)	NR

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NE, not estimable; NSCLC, non-small cell lung cancer; SD, standard deviation.
Notes: the company's efficacy set includes patients from ALKA, STARTRK-1 and STARTRK2 with ROS1-inhibitor naïve ROS1+ NSCLC, measurable disease at baseline and minimum 12-months' follow-up. The ERG's efficacy set includes patients with ROS1-inhibor naïve ROS1+ NSCLC and measurable disease at baseline who received entrectinib 600 mg (which could only be confirmed for STARTRK-2), with no minimum follow-up [a], Patients may have multiple sites of metastases at baseline; [b], Patients with history of CNS disease include those having prior surgery and/or radiation to the CNS, but not presenting with CNS lesions at baseline per the RECIST 1.1 Investigator assessment; [c], the definition of lines of therapy excluded (neo)-adjuvant and maintenance therapy. As a result, some patients that received chemotherapy were classified as having no previous lines of treatment.

10.3 Comparators not considered relevant from the NICE final scope

Chemotherapy in combination with a platinum drug for untreated disease

The NICE final scope lists docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with either carboplatin or cisplatin (otherwise known as platinum doublets) as a comparator. Most patients with ROS1+ NSCLC have non-squamous tumours so are eligible for pemetrexed maintenance therapy. The company asserts that platinum doublets are not commonly used in patients with non-squamous histology, and highlights that the committee for TA529 (crizotinib for ROS1+ NSCLC) concluded that they were not relevant comparators.

The ERG's clinical experts said that platinum doublets are used for non-squamous NSCLC when there are no known fusion proteins or mutations. However, they do not consider platinum doublets a relevant comparator for entrectinib because clinicians would only consider them for ROS1+ NSCLC late in the pathway when more effective targeted treatment options had been exhausted.

Single-agent third-generation chemotherapy for untreated disease

The NICE final scope lists single-agent chemotherapy as a comparator for patients who cannot tolerate a platinum-based therapy in a platinum doublet. The company asserts that newly diagnosed patients with ROS1+ NSCLC are generally young and physically fit and would be able to tolerate platinum-based therapy, and highlights that the committee for TA529 (crizotinib for ROS1+ NSCLC) concluded that they were not relevant comparators.

As for platinum doublets, the ERG's clinical experts do not consider single-agent chemotherapy a relevant comparator because clinicians would only consider using them for patients with ROS1+ NSCLC when more effective targeted treatment options had been exhausted.

Docetaxel with or without nintedanib after previous chemotherapy treatments (TA347)

The NICE final scope lists docetaxel as the only comparator after previous chemotherapy treatments, which can be given alone or in combination with nintedanib for patients with ROS1+ NSCLC and adenocarcinoma histology (which is the majority, see Section 2.1). The ERG's clinical experts advised that docetaxel is rarely used and agree with the company that it is not a relevant comparator because it would only be considered in the third-line or later setting.

Other treatments not in the NICE final scope that were highlighted by the ERG's clinical experts

The ERG's clinical experts highlighted that quadruple therapy with carboplatin, pemetrexed, bevacizumab and atezolizumab is now recommended as an option for non-squamous NSCLC, but can only be used for EGFR+ or ALK+ NSCLC when targeted therapy has failed (TA584).[27] The ERG sought advice from NICE about whether patients with ROS1+ NSCLC will be subject to the same condition regarding prior targeted therapy, in which case the quadruple therapy would be a relevant comparator for entrectinib after first-line crizotinib as an alternative to PEM+PLAT. However, the ERG does not consider it as a comparator for this STA because the recommendation was made after the NICE scope was finalised.

The immunotherapies atezolizumab and pembrolizumab are also listed in the NICE pathway for non-squamous NSCLC (including ROS1+ NSCLC) as alternatives to docetaxel with or without nintedanib, based on TA520 and TA428, respectively.[31, 32] The ERG notes that the recommendations are for patients who have received prior chemotherapy and, in the case of EGFR+ and ALK+ NSCLC, prior targeted

therapy as well. Regardless of whether patients with ROS1+ NSCLC would be subject to the same condition as EGFR+ and ALK+ patients regarding prior targeted treatment, the ERG does not consider the treatments relevant comparators for entrectinib because they would be used later in the treatment pathway (as explained above for docetaxel).

10.4 Prior systemic therapies

Table 56. Prior systemic therapies received in the ERG's entrectinib efficacy set (n =78) and PROFILE 1001 (study used to conduct the MAIC with crizotinib)

WHO ATC Level 4	ERG efficacy set for entrectinib (n = 78) N patients (%)	PROFILE 1001 crizotinib (n = 50) N patients (%)
Any platinum compounds	[redacted]	40 (80)
Cisplatin	[redacted]	-
Carboplatin	[redacted]	-
Any folic acid analogues	[redacted]	
Pemetrexed	[redacted]	36 (72)
Pemetrexed disodium	[redacted]	-
Pemetrexed disodium heptahydrate	[redacted]	-
Any monoclonal antibodies	[redacted]	-
Nivolumab	[redacted]	-
Bevacizumab	[redacted]	16 (32)
Lambrolizumab	[redacted]	-
Anetumab ravtansine	[redacted]	-
Any taxane	[redacted]	20 (40)
Paclitaxel	[redacted]	-
Docetaxel	[redacted]	-
Paclitaxel albumin	[redacted]	-
Any pyrimidine analogues	[redacted]	-
Gemcitabine	[redacted]	11 (22)
Gemcitabine hydrochloride	[redacted]	-
Gimeracil w/oteracil potassium/tegafur	[redacted]	-
Uftoral	[redacted]	-
Any protein kinase inhibitors	[redacted]	16 (32) erlotinib or gefitinib
Erlotinib hydrochloride	[redacted]	-
Crizotinib	[redacted]	-
Erlotinib	[redacted]	-
Afatinib	[redacted]	-
Gefitinib	[redacted]	-
Nintedanib	[redacted]	-
Tivantinib	[redacted]	-
Any podophyllotoxin derivatives	[redacted]	-
Etoposide	[redacted]	-
Any other antineoplastic agents	[redacted]	-
Other antineoplastic agents	[redacted]	-
Topotecan hydrochloride	[redacted]	-

Any vinca alkaloids and analogues	[redacted]	-
Vinorelbine	[redacted]	3 (6)
Any other drugs affecting bone structure and mineraliz	[redacted]	-
Denosumab	[redacted]	-
Any other therapeutic products	[redacted]	-
Investigational drug	[redacted]	-
All other therapeutic products	[redacted]	-
Any anthracyclines and related substances	[redacted]	-
Amrubicin hydrochloride	[redacted]	-
Any aromatase inhibitors	[redacted]	-
Letrozole	[redacted]	-
Any combinations of antineoplastic agents	[redacted]	-
Carboplatin w/gemcitabine	[redacted]	-

Abbreviations: ERG, evidence review group; MAIC, matching adjusted indirect comparison; N, number; WHO ATC, World Health Organization Anatomical Therapeutic Chemical Classification system.
Data for entrectinib were provided by the company at the clarification stage, and data for PROFILE 1001 are reported in the supplementary appendix to Shaw 2014.

10.5 Clinical effectiveness systematic literature reviews (SLRs)

The original searches for evidence in ROS1+ NSCLC populations were conducted in October 2018 and sought to identify clinical trials of any Phase, including single-arm studies, published from 2008 (CS Appendix D.1, Tables 1–3). The ROS1+ NSCLC searches were rerun in March 2019 with additional terms to identify observational studies (cohort, follow-up, epidemiologic and cross-sectional studies), and with no limit by publication date (systematic reviews limited to 2008 onwards). The original and update ALK+ NSCLC searches were run with the same strategies in February 2017 with no date restriction (CS Appendix D.1, Table 10) and October 2018 from 2017 onwards. The ERG considers that the sources searched (key bibliographic databases, recent conference proceedings, trial registries, key trial registries and HTA websites and systematic review reference lists), and terms used will have identified all relevant evidence to inform the decision problem of interest to this single technology appraisal (STA). The ERG considers the eligibility criteria for the ROS1+ SLR appropriate (CS Appendix, Table 10, reproduced in Table 57) and agrees that it is appropriate to seek only controlled clinical trials (randomised and non-randomised) and prospective studies from the ALK+ NSCLC SLR to focus on high quality evidence within the proxy population.

Table 57. Inclusion criteria for the company's SLRs (adapted from CS Appendix, Table 10)

Criteria	ROS1-positive NSCLC SLR: Include	ALK-positive NSCLC SLR: Include
Population	•Adult patients (18+) with ROS1+ advanced or metastatic NSCLC •Studies enrolling ROS1+ NSCLC patients specifically with brain/CNS metastases are also eligible. •Population can be any combination of chemotherapy-naïve or -experienced or TKI-naïve or -experienced in any treatment line within the advanced/metastatic setting	•Adult patients (18+) with ALK+ advanced or metastatic NSCLC •Studies enrolling ALK+ NSCLC patients specifically with brain/CNS metastases are also eligible. •Population can be any combination of chemotherapy-naïve or -experienced or TKI-naïve or -experienced in any treatment line within the advanced/metastatic setting

	•Further subgroups of interest: patients with brain metastases, Asian/non-Asian patients *Mixed populations* •For non-mutation specific populations, the ROS1+ subgroup data must be reported separately or at least 80% of patients must have ROS1+ NSCLC	•Further subgroups of interest: patients with brain metastases, Asian/non-Asian patients *Mixed populations* •For mixed lung cancer type (NSCLC/SCLC), at least 80% must be NSCLC •For mixed stage of disease, at least 80% must be advanced (IIIB) and/or metastatic (IV) •For non-mutation specific populations, the ALK+ subgroup data must be reported separately or at least 80% of patients must have ALK+ NSCLC
Interventions	•Entrectinib •Crizotinib •Pemetrexed + platinum chemotherapy •Pemetrexed •Docetaxel	•ALK-TKIs •Hsp90 inhibitors •Protein kinase B (Akt kinase/c c Akt protein) inhibitors •Taxanes: docetaxel, paclitaxel •Pemetrexed, gemcitabine, cisplatin, carboplatin, vinorelbine •Immunotherapies •Checkpoint inhibitors •Insulin-like growth factor receptor antibodies •EGFR inhibitors •Bevacizumab
Comparators	All studies that contain one of the interventions of interest in at least one study arm will be included regardless of comparator	
Outcomes	Studies reporting at least one outcome of interest as a primary or secondary outcome (full list in CS Appendix Table 10 – all efficacy and safety outcomes in the NICE final scope listed)	
Setting/study design	•Randomised controlled trials (Phase II–IV) •Non-randomised controlled trials •Prospective single-arm trials •Prospective ongoing trials to investigative one active treatment •No restriction on blinding •Observational studies	•Randomised controlled trials (Phase II–IV) •Non-randomised controlled trials •Prospective single-arm trials •Prospective ongoing trials to investigative one active treatment •No restriction on blinding
Language of publication	None	
Date of publication	2008 - present	No restriction

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CR, complete response; DoR, duration of response; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; SAE, serious adverse event; SD, stable disease; SLR, systematic literature review; TTR, time to response.
a, At the time of SLR update, studies reported/conducted in ALK+, EGFR+ or mutation other than ROS1 NSCLC were excluded and flagged at primary screening stage. This assumed that there are rare incidences/possibility of co-mutations and the NSCLC patients with co-mutations were not of interest for this SLR; b, see CS Appendix Table 10 for specific treatments.

Twenty studies were considered relevant to UK clinical practice (11 in ROS1+ NSCLC populations and 9 in ALK+ NSCLC populations), and a narrative feasibility assessment presented in the submission considered 11 of these for the MAIC. The ERG did not consider the process of selecting PROFILE 1001, ASCEND-4 and PROFILE 1007 for the MAICs transparent and requested further justification at the clarification stage. Reasons for exclusion were provided for the 11, 34 and 25 studies that met the eligibility criteria for ROS1+ SLR (original and update combined), original ALK+ SLR, and update ALK+ SLRs, respectively (CS Appendix D.1, Figures 1–3), as well as more details of the feasibility assessment for the MAICs. After reviewing reasons for exclusion, the ERG considers it reasonable that the company focused on studies of treatments relevant to the decision problem and is satisfied that no relevant studies were excluded from the 20 studies considered in more detail. However, some of the

reasons for excluding studies from the 20 assessing treatments relevant to UK clinical practice may not be justified (provided at clarification and summarised in Table 58). Information provided by the company shows that most of the 11 ROS1+ studies considered for the MAICs were unsuitable for an MAIC because treatment was not well defined, insufficient baseline data were available to perform matching, or because data were not available for key outcomes (Table 58). However, the ERG notes that some studies that may have been suitable were excluded for reasons that are also true for the entrectinib dataset, such as immature OS and a high level of prior treatment within the population.

Table 58. Studies included in the company's ROS1+ and ALK+ systematic literature review (SLR) that were considered for the MAIC

Study ID	Location	Study design	Population and prior treatment	Intervention	Relevant endpoints	Median FU (m)	Reason(s) for exclusion from MAIC
Studies of ROS1+ NSCLC							
PROFILE 1001 (NCT00585195)[37]	Multicentre	Phase I, OL, single-arm	Mixed naïve and pre-treated – 86% had received 0 or 1 prior treatment	Crizotinib	OS; PFS; TR; safety	16.4	**Chosen for MAIC of entrectinib vs crizotinib**
AcSe[41] (NCT02034981)	France, multicentre	Phase II, OL, single-arm	Mixed naïve and pre-treated – 0 or 1 prior treatment incl. platinum- doublet, unless unfit for chemo (n = 37)	Crizotinib	OS; PFS; TR;	NR	Most/all received crizotinib at 2L+, OS KM data immature, PFS inconsistent across reports
METROS [77] (NCT02499614)	Italy, multicentre	Phase II, OL, single-arm	Mixed naïve and pre-treated – 0 or 1 previous standard chemotherapy regimen (no recruitment yet)	Crizotinib	OS; PFS; TR; safety	NR	Abstract, insufficient data to conduct MAIC
OxOnc[42] (NCT01945021)	East Asia, multicentre	Phase II, OL, single-arm	Mixed naïve and pre-treated – ≤3 lines of systemic therapy for advanced disease (n = 127)	Crizotinib	OS; PFS; TR; safety; PROs	NR	Most/all received crizotinib at 2L+, OS KM unavailable, East Asian population
EUROS1[44]	Europe, multicentre	Retrospective, observational	Mixed naïve and pre-treated – 0 or 1 prior chemo (n = 32 but 1 received crizotinib)	Crizotinib	OS; PFS; TR; safety	NR	Most received crizotinib at 2L+ (41.9% at 5L); OS not reported
Bennati 2015[78]	Italy	Retrospective observational	Mixed naïve and pre-treated – 0 or 1 prior treatment incl. platinum- doublet, unless unfit for chemo (n = 10)	Crizotinib	OS; PFS; TR;	NR	Abstract, insufficient data to conduct MAIC
Zhang 2016[79]	China, single centre	Retrospective, observational	Pre-treated – prior crizotinib or chemo (pemetrexed or non-pemetrexed) (n = 51 but only 15 had crizotinib)	Crizotinib	PFS; TR	NR	Treatment details unclear, small sample, effects by line and OS not reported
Chen 2016[80]	single centre	Retrospective, observational	Prior treatment not reported (n = 19)	Pemetrexed versus PEM+PLAT	OS; PFS; TR;	14.1	Small sample, younger than entrectinib population (43.8 yrs), mix of treatments and lines
Scheffler 2015[81]	Single-centre	Retrospective, observational	Pre-treated – prior chemo (n = 19)	Crizotinib	OS; TR	16.6	Treatment details unclear, small sample, PFS and effects by line NR, OS immature.
Zhang 2018[82]		Retrospective, observational	Pre-treated – prior platinum-doublet as palliative treatment (n = 55)	Pemetrexed vs non-pemetrexed chemo	PFS; TR;	NR	Abstract, insufficient data to conduct MAIC

Patil 2018[83]	single centre	Retrospective, observational	Prior treatment not reported (n = 33)	Crizotinib	PFS; CNS	30	Treatment details unclear, OS not reported, all had CNS disease
Studies of proxy population with ALK+ NSCLC							
ASCEND-4[70] (NCT01828099)	Multicentre	Phase III, OL RCT	Treatment-naïve – no prior systemic anticancer therapy, except neoadjuvant/adjuvant	Ceritinib vs PEM+PLAT with PEM maintenance	OS; PFS; TR; PRO; CNS; safety	NR	**Chosen for MAIC as a secondary analysis of entrectinib vs PEM+PLAT**
PROFILE 1014[50] (NCT01154140)	Multicentre	Phase III, OL RCT (crossover at PD allowed)	Treatment-naïve	Crizotinib vs PEM+PLAT	OS; PFS; TR; safety; PROs	17	**HRs applied to results from entrectinib vs crizotinib MAIC to estimate PEM+PLAT. Not chosen for MAIC because no PEM maintenance.**
PROFILE 1007[51] (NCT00932893)	Multicentre	Phase III, OL, RCT	Pre-treated – one prior platinum chemo, no crizotinib	Crizotinib vs pemetrexed or docetaxel	OS; PFS; TR; safety; PROs	12.2	**Used for MAIC of entrectinib vs docetaxel after prior chemo**
ALEX[84] (NCT02075840)	Multicentre	Phase III, OL, RCT	Treatment naïve	Alectinib vs crizotinib	OS; PFS; TR; CNS; safety	18.6 alect; 17.6 crizo	Evidence available for crizotinib in ROS1+ NSCLC so proxy population not required
J-ALEX[54] (JapicCTI-132316)	Multicentre	Phase III, OL RCT	Mixed naïve and pre-treated – no prior ALK-TKI, no prior chemo (64%) or 1 chemo (36%)	Alectinib vs crizotinib	OS; PFS; TR; satefy; CNS	12.0 alect; 12.2 crizo	Evidence available for crizotinib in ROS1+ NSCLC so proxy population not required
ALTA-1L[85] (NCT02737501)	Multicentre	Phase III, OL RCT	Mixed naïve and pre-treated – 0 or 1 prior systemic therapy, no prior ALK-TKI	Brigatinib vs crizotinib	PFS; TR; safety; CNS	11.0 brig; 9.3 crizo	Evidence available for crizotinib in ROS1+ NSCLC so proxy population not required
PROFILE 1029[73] (NCT01639001)	Multicentre	Phase III, OL RCT (crossover at PD allowed)	Treatment-naïve	Crizotinib vs PEM+PLAT	OS; PFS; PROs; safety	22.5 crizo; 21.6 chemo	East Asian population; no PEM maintenance so ASCEND-4 preferred.
ALUR[86] (NCT01828099)	Multicentre	Phase III, OL, RCT	Pre-treated – prior platinum-doublet chemo and crizotinib	Alectinib vs pemetrexed or docetaxel	OS; PFS; TR; CNS; safety	6.5 alect;; 5.8 chemo	Small sample (n = 35) and short follow-up (~6 months) so PROFILE 1007 preferred.
ASCEND-5[72] (NCT01828112)	Multicentre	Phase III, OL, RCT	Pre-treated – 1-2 lines of chemo and crizotinib	Ceritinib vs pemetrexed or docetaxel	OS; PFS; TR; safety; PROs	16.5	Mix of 2L and 3L and only 2L of interest so PROFILE 1007 preferred.

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system progression outcomes; KM, Kaplan-Meier curve; MAIC, matching adjusting indirect comparison; NR, not reported; NSCLC, non-small-cell lung cancer; OL; open-label; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; TR, tumour response (including objective response, time to response etc.)
Note: information from Appendix D.1 of the company's submission and the company's response to clarification.

10.6 Quality assessment

Table 59. Company's Downs and Black quality assessment of the entrectinib ROS1+ integrated analysis (with validation from the ERG) and PROFILE 1001

	Entrectinib integrated analysis		PROFILE 1001 (company)
Question	**Company response**	**ERG comment**	
Reporting			
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes for STARTRK-2, but uncertainties about dose in ALKA and STARTRK-1	Yes
Are the distributions of principal confounders in each group of patients to be compared clearly described?	N/A	Discussed with regard to the MAICs	Yes
Are the main findings of the study clearly described?	Yes	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	No	No	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes, treatment-related AEs occurring in a minimum of 2% of patients were reported along with all common AEs occurring in at least 10% of patients. However, it should be noted that a different analysis set was used for the AE results to the efficacy outcomes with the AEs data from a broader patient population.	Yes
Have the characteristics of patients lost to follow-up been described?	No	No	No
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?	N/A	No, formal significance tests were not performed	Yes
External validity			
Were the patients asked to participate in the study representative of the entire population from which they were recruited?	Yes	Yes – as confirmed by clinical experts	Yes
Were those patients who were prepared to participate representative of the entire population from which they were recruited?	Yes	Yes – as confirmed by clinical experts	Yes
Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes	Unknown	Yes
Internal validity – bias			

Was an attempt made to blind study patients to the intervention they received?	No	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	Yes, as BICR was used for assessment of ORR and PFS although this was done retrospectively for ALKA and STARTRK-1 (prospective in STARTRK-2).	No
If any of the results of the study were based on 'data dredging', was this made clear?	N/A	N/A	Yes
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	N/A as single arm studies, however, patients with less than 12 months follow-up were excluded from the analyses.	N/A
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes
Was compliance with the intervention(s) reliable?	Yes	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes
Internal validity – confounding (selection bias)			
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?	N/A	N/A	N/A
Were study patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A	N/A	N/A
Were study patients randomised to intervention groups?	N/A	N/A	No
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	N/A	N/A
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N/A	N/A	Yes
Were losses of patients to follow-up taken into account?	Primary outcome of ORR was assessed through BICR to minimise bias	Patients with less than 12 months follow-up were excluded from the analyses.	Yes
Power			
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N/A Power was sufficient to detect a clinically meaningful response	Not for key survival outcomes. Power calculation based on ORR.	Not assessed

Abbreviations: AEs, adverse events; BICR, blinded independent central review; N/A, not-applicable; ORR, objective response rate. Compiled from CS Appendix D.3, Table 28 and D.1, Table 26.

10.7 Participant flow

Table 60. Participant flow in the entrectinib trials (reproduced from CQ response, Table 1)

	ALKA	STARTRK-1	STARTRK-2	STARTRK-NG	TOTAL
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Screen Fail	0	0	15	0	15
Enrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: not dosed	1	0	1	0	2
Safety population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROS1+ NCSLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Prior ROS1 inhib	0	10	17	0	27
--Excluded: Other	0	0	4	0	4
ROS1+ NCSLC Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
--Excluded: Non-Measurable Disease (>12m FUP)	2	1	0	0	3
--Excluded: Non-Measurable Disease (<12m FUP)	0	0	6	0	6
ROS1+ NCSLC Efficacy Evaluable (explore)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled prior April 30, 2017 (>12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Enrolled after April 30, 2017 (<12m FUP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FUP, follow-up; NSCLC, non-small-cell lung cancer.

10.8 Quality of life results from the entrectinib studies

Patient reported outcome (PRO) data for entrectinib are only available from the STARTRK-2 study, because they were not measured in the Phase I trials. The ERG efficacy set is restricted to STARTRK-2 for all outcomes, and so the difference in numbers between the ERG efficacy set (n = 78) and company efficacy set (n = 37) for the quality of life outcomes is a result of the 12-month follow-up restriction only. Results for the EORTC-QLQ-30,[38] a generic cancer quality of life measure, and the lung cancer specific QLQ-LC13[39] module are shown in Table 61. Results for the EQ-5D, which was administered as a generic quality of life measure in STARTRK-2, are covered in Section 5.3.7.

Data were collected prior to any dosing of entrectinib, on day 1 of each visit (starting at the first cycle), and at the end of treatment (EoT; CS, page 28). Completion rates reported in the original submission for the company's efficacy set show high rates for the QLQ-C30 and QLQ-L13 at baseline ([redacted]% and [redacted]%, respectively) that remained above 80% at most study visits but dropped to [redacted]% by week 20.

The company consider the QLQ-C30 scores to show moderate-to-high functioning at baseline in line with the ECOG performance status eligibility (0 or 1), and the QLQ-LC13 scores to show moderate lung cancer specific symptom burden at baseline (Table 61). Baseline scores are similar for the company and ERG efficacy sets.

The company's description of results highlighted particular time points where some scores peaked (e.g. improvement in severe cough after the first dose) or showed marked deterioration but, in general, the company considered the data to show maintained or improved quality of life from baseline to the end of treatment. It should be noted that reductions between baseline and end of treatment indicate worsening for global health status and physical, role and cognitive functioning, but increases indicated worsening for all symptom-related scales.[38, 39] With this and a minimal clinically important difference (MCID) of 10 in mind, the ERG considers there to be some indication of deterioration in global health status, functioning and symptom domains of the EORTC QLQ-C30 (Table 61); however, the variation between means and medians in each efficacy set and the large SDs and ranges suggest a great deal of variation within the population.

Scores were more stable for symptoms reported in the EORTC LC-13, with only dyspnoea showing a clear sign of worsening between baseline and the end of treatment (Table 61). The ERG notes that several items of the LC13 were omitted from the results, most of which relate to treatment-related side effects (haemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia).

Table 61. Quality of life for the company and ERG efficacy sets

		Company STARTRK-2 efficacy set (n = 37)		ERG efficacy set (n = 78)	
Score	**statistic**	**Baseline**	**Change from baseline to EoT**	**Baseline**	**Change from baseline to EoT**
EORTC QLQ-C30					
Global Health Status (higher better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Physical Functioning (higher better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Role Functioning (higher better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive Functioning (higher better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea (lower better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue (lower better)	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-LC13					
Coughing	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]

	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in arm or shoulder	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in chest	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in other parts	Mean (sd)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CQ, clarification questions; EORTC-QLQ-30, European Organization for Research and Treatment Quality of Life Core Questionnaire; EORTC-QLQ-LC13, EORTC lung cancer module (QLQ-LC13); EoT, end of treatment; ERG, evidence review group; sd, standard deviation.
Data from CS Tables 12 and 13 and company's response to clarification Table 11.

10.9 Subgroup analyses

Patients with and without CNS disease at baseline were the only subgroups of interest listed in the NICE final scope. Subgroup analyses for key efficacy outcomes were submitted for the company's primary efficacy analysis and were provided for the ERG's preferred analysis at the clarification stage, but subgroups are not reflected in the economic model. The ERG notes that the presence of CNS metastases at baseline was determined by the investigator for subgroup analyses (CS, page 28). Specific CNS-related endpoints assessed for all patients and for patients with CNS disease at baseline are presented in Section 4.3.4.

Statistical significance tests were not conducted to compare patients with and without CNS disease at baseline. Nonetheless, the subgroup results suggest that PFS is likely to be [redacted] and response rates [redacted] for patients with CNS disease than those without CNS disease at baseline (Table 62). The reason for far more pronounced differences in PFS and DOR for patients with no CNS compared to those with CNS disease at baseline in the company's preferred analysis (PFS [redacted] versus [redacted] months; DoR [redacted] versus [redacted] months) than ERG's preferred analyses is not clear. The ERG highlights that all subgroup analyses are based on small numbers of events and, for OS, immature survival follow-up.

Table 62. Key efficacy endpoints (BICR) by presence of CNS disease at basline

	Company's integrated analysis (n = 53)				**ERG's preferred analysis (n = 78)**	
CCOD for enrolment	**31 May 2018**		**30 Oct 2018**		**301 May 2018**	
Baseline CNS disease	**No (n = 30)**	**Yes (n = 23**	**No (n = 30)**	**Yes (n = 23**	**No (n = 43)**	**Yes (n = 35)**
Overall survival						
Patients with event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival						
Patients with event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median, months (95% CI)	[redacted]					
Objective response[a]						
Patients with response, n (%)	[redacted]					
95% CI for response	[redacted]					
Duration of response[c]						
Median months (95% CI)	[redacted]					

Abbreviations: BICR, blinded independent central review; CI, confidence interval; NE, not estimable.
Data compiled by the ERG from CS Table 7 and company response to clarification Table
Notes: a, Objective response is defined as PR or CR confirmed by repeat-imaging at least 28 days following first documentation of response. Otherwise, the patient is considered to be a non-responder; b, Best Overall Response is derived per RECIST 1.1; c, Median DOR was estimated using KM methods and measures of time from first response to death or progressive disease (censored at the last tumour assessment); CIs are calculated using the Clopper-Pearson method; d, median was extended due to censoring date changes in the later CCOD.

The ERG's clinical experts indicated that prior TKI use may be an important effect modifier, and so the ERG requested a subgroup analysis to compare OS, PFS and ORR for patients who had ([redacted]) and had not received a prior TKI ([redacted]). A full breakdown of prior therapies received by patients included in the ERG's preferred analysis were provided in the company's response to clarification (see Appendix 10.3). Of note, [redacted] patients enrolled in the entrectinib trials had received a prior ROS1-targeted TKI and were excluded from the company's and the ERG's preferred efficacy sets (see Section 3.1). Results for the prior TKI subgroup analysis shown in Table 63 do not suggest an important difference between subgroups.

Table 63. Subgroup analysis to explore prior TKI use - ERG efficacy set (reproduced from CQ response Table 15)

Endpoint (model)	**No prior TKI**		**Prior TKI**		**Effect of prior TKI vs no prior TKI**	
	n patients	**n events/ responses**	**n patients**	**n events/ responses**	**OR/HR**	**p-Value (LRT)**
ORR (logistic regression)	[redacted]					
PFS (cox model)	[redacted]					
OS (cox model)	[redacted]					

Abbreviations: HR, hazard ratio; LRT, likelihood ratio test; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Results of a range of additional predefined subgroup analyses conducted on the company's primary analysis of ORR by BICR were provided in Appendix E of the CS, which have not been reproduced by the ERG. ORR ranged from [redacted] to [redacted] across individual subgroups for entrectinib dose (below 600 mg, 600 mg and above 600 mg), ECOG performance status (0, 1, 2, ≥3), and a range of subgroups to explore type and number of prior anticancer therapies (systemic, chemotherapy, targeted, hormonal, radiation, surgery and brain radiation). The ERG does not consider there to be a sufficient number of patients to draw any meaningful conclusions about subgroup differences.

10.10 Adverse events from the entrectinib ROS1+ and total safety sets

Adverse event data for entrectinib were submitted for the ROS1 safety set ([redacted] patients with ROS1+ NSCLC who had received at least one dose of entrectinib in ALKA, STARTRK-1 and STARTRK-2) and the total safety set (n=[redacted]; any patient who received any dose of entrectinib in STARTRK-NG, ALKA, STARTRK-1 and STARTRK-2), but the company used data for their preferred efficacy set to reflect selected Grade 3 and 4 events in the economic model (see Section 5.3.6). The ERG's summary and critique of the adverse event data for the ROS1 safety set and total safety set are provided under the following headings.

10.10.1 Treatment exposure

The company provided details of entrectinib exposure in all three safety analysis sets and the ERG notes that median treatment duration, median number of cycles and mean cumulative dose were consistently [redacted] in the ERG efficacy set and ROS1 safety set compared to the total safety population (Table 64). These data therefore suggest that the ROS1 patients had exposure to entrectinib over a [redacted] period of time (median [redacted] months) compared to the Total safety population (median [redacted] months). It is not possible to comment on any potential difference in entrectinib daily dose between the analysis sets.

Table 64. Summary of extent of exposure to entrectinib in the ROS1 safety population and all patients treated with entrectinib (adapted from CS, Table 28 and CQ response Table 12)

	ERG efficacy set (n = 78)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Median treatment duration, months (range)[a]	[redacted]	[redacted]	[redacted]
Median no. of cycles (range)	[redacted]	[redacted]	[redacted]
Median no. of missed doses (range)	[redacted]	[redacted]	[redacted]
Mean cumulative dose, mg (SD)	[redacted]	[redacted]	[redacted]
Median dose intensity, % (range)[b]	[redacted]	[redacted]	[redacted]

Abbreviations: SD, Standard Deviation.
Notes: a, Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day; b, defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity □100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

10.10.2 Adverse events

There were no specific adverse events (AEs) of interest specified in the NICE final scope although adverse events were listed as an outcome. The ERG notes that the company have provided comprehensive AE data in the CS and its appendices for the ROS1 safety population and Total safety population. In addition, a draft summary of product characteristics (SmPC) was submitted by the company as Appendix C of the company submission and this contained further supplementary information on AE's for the total safety population. The SmPC also detailed that the [redacted]

[redacted]

Table 65 provides an overview of the AEs for the ROS1 safety population and the total safety population. AE rate's in the total safety population were [redacted] compared to those in the ROS1 safety population although this may be a reflection in the differences in treatment exposure between the two analysis sets.

[redacted] ROS1+ patients ([redacted]) experienced at least one AE, and [redacted] experienced an AE that was considered to be related to treatment. Grade 3 or higher AEs occurred in [redacted] of the ROS1+ patients and [redacted] of patients had a treatment-related Grade 3 or higher AE. Further details on the treatment-related AE's are provided in Section 10.10.3. Table 32 in the CS provides details of the Grade 3 or higher AEs reported in ≥2% of patients in the ROS1 safety population and in the total safety population; the most frequently reported Grade 3 or higher AEs were weight increased ([redacted]%), dyspnoea ([redacted]%), urinary tract infection ([redacted]%), alanine aminotransferase increased ([redacted]%), pulmonary embolism ([redacted]%), neutropenia ([redacted]%) and pneumonia ([redacted]%).

AEs led to dose interruption in [redacted] of ROS1+ patients and dose reduction in [redacted] of ROS1+ patients (Table 65). The most common AEs resulting in the dose interruptions were dizziness ([redacted]%), cognitive disorder ([redacted]%), blood creatine increased ([redacted]%), dyspnoea ([redacted]%), and pleural effusion ([redacted]%). AEs leading to discontinuation of entrectinib were reported in [redacted] of ROS1+ patients (Table 65) and were most commonly a result of respiratory, thoracic and mediastinal disorders ([redacted]%), gastrointestinal disorders ([redacted]%), cardiac disorders ([redacted]%), and nervous system disorders ([redacted]%). Further details of the AEs leading to withdrawal, dose interruption or dose reduction is provided in the CS, Appendix L.6.

A summary of fatal AEs in the ROS1 safety population and in the total safety population is provided in the CS, Appendix L.6. There were no treatment-related deaths with entrectinib in either analysis set although fatal AEs (Grade 5 AEs) occurred in [redacted]% of patients in the ROS1 safety population and in [redacted]% of patients in the total safety population (Table 65).

Table 65. Overview of adverse events in the ROS1 safety population and in all patients treated with entrectinib (reproduced from CS, Table 29)

	ROS1 safety population (n=[redacted])	**Total safety population (n=[redacted])**
Any AE	[redacted]	[redacted]
Treatment related AEs	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]
Serious treatment related AEs	[redacted]	[redacted]
Grade ≥3 AEs	[redacted]	[redacted]
Grade ≥3 treatment related AEs	[redacted]	[redacted]

AEs Leading to Discontinuation	[redacted]	[redacted]
Treatment related AEs Leading to Discontinuation	[redacted]	[redacted]
AEs Leading to Dose Reduction	[redacted]	[redacted]
Treatment related AEs Leading to Dose Reduction	[redacted]	[redacted]
AEs Leading to Drug Interruption	[redacted]	[redacted]
Treatment related AEs Leading to Drug Interruption	[redacted]	[redacted]
AEs Leading to Death	[redacted]	[redacted]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0; includes AEs with start date on or after the date of first dose of study treatment and up to and including 30 days after the last dose of study treatment, or events with start date prior to the date of first dose of study treatment and worsened in severity or become serious during treatment.

The company provided a breakdown of AEs that occurred in ≥10% of patients in the ROS1 safety population or total safety population in the CS, Table 30. The most common AEs in ROS+ patients were constipation ([redacted]%), dysgeusia ([redacted]%), dizziness ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), dyspnoea ([redacted]%), oedema peripheral ([redacted]%), fatigue ([redacted]), nausea ([redacted]%) and cough ([redacted]%). Results in the total safety population were in keeping with those of the ROS1 population.

10.10.3 Treatment related adverse events

The most frequently reported treatment related AEs in the ROS1+ population (Table 66) were dysgeusia ([redacted]%), dizziness ([redacted]%), constipation ([redacted]%), diarrhoea ([redacted]%), weight increase ([redacted]%), and fatigue ([redacted]%). These AEs are generally reflective of the most commonly occurring AEs in the entrectinib studies although the ERG notes that none of the respiratory AEs (e.g. dyspnoea and cough) were deemed to be treatment-related. [redacted] treatment-related AE rates were reported in the total safety population as for the ROS1 safety population (Table 66).

Table 66: Treatment related AEs reported by ≥10% of patients in the ROS1 safety population or in all patients treated with entrectinib (reproduced from CS, Table 31)

AE, n (%)	ROS1 safety population (n=[redacted])	Total safety population (n=[redacted])
Any treatment related AE	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Investigations	[redacted]	[redacted]

Weight increased	[redacted]	[redacted]
Blood creatine increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes: Investigator text for AEs encoded using MedDRA version 21.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For
frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

10.10.4 Serious adverse events

Serious AEs (SAEs) were reported in [redacted]% of ROS1-positive patients and [redacted]% of patients had SAEs that were considered to be treatment-related (Table 67). The most frequently reported SAEs were pneumonia ([redacted]%), dyspnoea ([redacted]%) and pyrexia ([redacted]%) although it should be noted that these data relate to all SAEs and not just those deemed to be treatment-related. The ERG also notes that the SAEs reported in ≥2% of patients in the ROS1 safety population or total safety population were not among the most commonly reported as treatment-related AEs (i.e. those occurring in ≥10% of patients). Similar SAE rates were reported in the total safety population to those in the ROS1 safety population (Table 67).

Table 67: Serious adverse events reported in ≥2% of patients in the ROS1 safety population or in all patients treated with entrectinib (reproduced from CS, Table 33)

AE, n (%)	**ROS1 safety population (n=[redacted])**	**Total safety population (n=[redacted])**
Any serious AEs	[redacted]	[redacted]
Respiratory thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Notes**:** Investigator text for AEs encoded using MedDRA version 21.0.
Percentages are based on N in the column heading. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For
frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately

10.10.5 Other adverse events

The ERG notes from the draft SmPC that [redacted]

Table 68. Entrectinib treatment-emergent changes from baseline in key laboratory abnormalities (reproduced from draft SmPC, Table 6).

[redacted]	[redacted]	
	[redacted]	[redacted]
Chemistry		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hematology		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
Notes: 1, Based on number of patients with available baseline and at least one on-treatment test value; 2, N=339 for Blood Creatinine, AST and ALT; N=332 for Neutrophils; N=346 for Haemoglobin; 3, Patients with change from baseline values of Grade of 0−2 to a post−baseline value of Grade 3 or Grade 4 at any time

10.11 Potential benefits for CNS disease

At the time of the company's primary entrectinib analysis, [redacted] of patients had either died ([redacted]) shown progression of an existing CNS lesion ([redacted]) or shown evidence of a new CNS lesion ([redacted]), and similar proportions are seen in the ERG's preferred analysis (Table 69). Median time to CNS progression regardless of baseline CNS disease was [redacted] in the company's analysis and was [redacted] months in the ERG's preferred analysis (95% CI [redacted]).

A similar proportion of the company and ERG efficacy sets had CNS metastases at the start of treatment ([redacted], respectively) and, among these patients, [redacted] had either died or shown CNS progression in the ERG's preferred analysis ([redacted]) than in the company's preferred analysis ([redacted]; Table 69). Median time to intracranial progression was similar ([redacted] months, respectively).

Measures of intracranial response to entrectinib for patients with CNS disease at baseline in the company's analyses showed that [redacted] of patients showed a complete ([redacted]) or partial response ([redacted]) to treatment (repeat scans show durability of at least 28 days from first response; Table 69), and median duration of intracranial response was approximately a year ([redacted] months, 95% CI [redacted]). Results

for intracranial response in the ERG's preferred analysis were consistent with the company's integrated analysis (Table 69).

Table 69. Intracranial outcomes with entrectinib (BICR using RECIST v1.1)

	Company's integrated analysis (n = 53)		ERG's preferred analysis (n = 78)
CCOD for enrolment	**31 May 2018**	**30 Oct 2018**	**31 May 2018**
Time to CNS progression (all patients regardless of baseline CNS disease)			
Patients with event	[redacted]	[redacted]	[redacted]
First event CNS progression	[redacted]	[redacted]	[redacted]
First event first new lesion in CNS	[redacted]	[redacted]	[redacted]
First event death	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]
Intracranial PFS (patients with baseline CNS mets)			
Patients with baseline CNS disease, n (%)	[redacted]	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
First event progression	[redacted]	[redacted]	[redacted]
First event death	[redacted]	[redacted]	[redacted]
Patients without event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]
Intracranial response (CR or PR on repeat scans at least 28 days apart - patients with baseline CNS mets)			
Patients with response, n (%)	[redacted]	[redacted]	[redacted]
95% CI for response	[redacted]	[redacted]	[redacted]
Best objective intracranial response, n (%)			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease[a]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Non-complete or partial response[a,b]	[redacted]	[redacted]	[redacted]
Missing or unevaluable[c]	[redacted]	[redacted]	[redacted]
Duration of intracranial response			
Median months (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; ERG, evidence review group; n, number of patients; PR, partial response; RECIST, response evaluation criteria for solid tumours.
Data compiled by the ERG from CS Tables 10 and 15 and company response to clarification Tables 10 and 17.
Time to CNS progression included all patients in the analysis and was defined as the time from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause; Intracranial PFS included only patients with CNS disease at baseline (measurable or unmeasurable) and was defined as the time from first dose of entrectinib to CNS tumour progression or death due to any cause
a, SD and Non-CR/Non-PD must be observed study day 35 or later, otherwise they count as NE; b, Patients were categorised as having Non CR/PD if they had non-target lesions, but had measurable disease at baseline as assessed by Investigator; c, Missing or unevaluable category includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response; CIs calculated with Clopper-Pearson method.

10.12 Critique of the MAIC methods

The company describe the methods of performing the MAICs in Section B.2.9 of the CS and stated that the same approach was taken to the MAICs conducted at the request of the ERG. Briefly, the company explain that entrectinib-treated patients are assigned statistical weights derived by MAIC, which is a form of propensity score weighting. A propensity score logistic regression model estimates the odds of being enrolled into the entrectinib cohort or the comparative evidence source, and average baseline characteristics (mean and variance) can then be balanced between the selected entrectinib cohort and the comparator population. After the matching procedure had been conducted and the weights derived, efficacy outcomes were compared between balanced treatment groups using statistical tests that incorporate the derived weights (CS Appendix, pg. 72). Ultimately, the method adjusts the amount of weight patients in the entrectinib population are given in the analysis to rebalance the effect of known treatment modifiers. Unanchored MAICs (where there is no common treatment arm in studies being compared) can only account for known differences in the populations where baseline data are available and may be confounded by unmeasured or unknown differences between study populations.

For OS and PFS, weighted KM curves were generated and HRs between treatments estimated using weighted Cox proportional hazards models. For ORR and treatment discontinuation due to adverse events (AEs), odds ratios (OR) between treatments were estimated using the derived weights. Planned analyses for any serious adverse event could not be conducted because they were only reported for entrectinib, and analyses for any Grade 3+ adverse event were not conducted because the threshold for reporting varied from 2% to 15% across studies (CS, Table 18). The company outlined that a bootstrap estimator was used to account for within-patient correlation introduced by the use of weights (Appendix, pg. 72), which gives a distribution of effect sizes to generate CIs.

The company state that the MAICs were conducted in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[87] However, the analyses only adjusted for a selected set of effect modifiers and prognostic variables, and so the ERG requested that all effect modifiers and prognostic variables were adjusted as recommended in TSD 18.[87] In their response, the company noted that the selection of covariates adjusted for were informed by clinical expert opinion about important prognostic and effect modifiers. The company also explained that an attempt was made to limit the number of covariates for adjustment in light of the small sample sizes in ROS1+ NSCLC studies. The company explain that weighting always reduces the effective sample size, and a large reduction from sample size to effective sample size is an indication that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable. The company did not attempt to quantify systematic error in accordance with TSD 18 but provided a rationale for not doing so in their response to clarification (namely that there was insufficient evidence to estimate between study variance for the out of sample method, and the in-sample cross-validation method is not appropriate for MAICs).[87]

10.12.1 Matching procedure for entrectinib versus crizotinib

The company used their primary integrated analysis of entrectinib at the 31 May 2018 CCOD as the basis for their preferred MAICs with PROFILE 1001. Data for the later CCOD including patients enrolled up to 30 October 2018 were available for the company's preferred efficacy set, but the company chose not to use the later data cut for their base case. Despite outlining in their submission that a longer follow-up for PROFILE 1001 was published after the MAIC had been conducted (Shaw 2019[46]), the company did not update its base case with the Shaw 2019 data for the crizotinib MAIC. The ERG's preferred MAIC for entrectinib versus crizotinib is based on the ERG efficacy set for entrectinib (patients enrolled up to 31 May 2018 receiving 600mg dose of entrectinib with no minimum follow-up) and the longer follow-up data for crizotinib in PROFILE 1001 from Shaw 2019.

In each MAIC to derive estimates for entrectinib versus crizotinib, the entrectinib population was reweighted according to the following population characteristics in PROFILE 1001: sex, race (Asian vs non-Asian), ECOG (0 vs 1 or 2), smoking history, prior treatments (treatment naïve vs prior treatment), age and disease stage (Stage IIIB vs Stage IV non-CNS metastasis vs Stage IV CNS metastasis).

While the choice of factors was not justified fully, the ERG could only find additional baseline data for histology in PROFILE 1001, which was very similar between PROFILE 1001 and the ERG's preferred population (>97% adenocarcinoma). However, the ERG notes from the reweighted baseline characteristics presented by the company that disease stage, including the presence of CNS metastases, was not included as a baseline characteristic for matching. The ERG could not find the data in any of the publicly available publications for PROFILE 1001, and the data were listed as not reported in the committee papers for TA529 (for which PROFILE 1001 is the primary evidence source). Nonetheless, disease stage at baseline and the presence of CNS metastases at baseline in particular are likely to be key effect modifiers which could not be included as covariates.

Before reweighting, a higher proportion of entrectinib-treated patients had ECOG performance status of 2 ([redacted] and [redacted] depending on the choice of efficacy set versus 1.89% in PROFILE 1001), and a lower proportion were never smokers ([redacted] and [redacted] versus 75.47%). The ERG understands that the higher proportion of patients in the ERG's efficacy set shown as being treatment naïve ([redacted]) is because the proportion who have received no prior systemic therapy has been used rather than the proportion with no prior therapy; the equivalent proportion who received no prior systemic therapy in the company's efficacy set is [redacted] (see Appendix 10.2 for full baseline characteristics before reweighting). Weighted patient characteristics for the company and ERG efficacy sets following the matching procedures are shown with characteristics for the PROFILE 1001 crizotinib population in Table 70, which indicates that the study populations have been matched successfully for the chosen

characteristics. The distribution of weights and effective sample size for each variable was provided in the company's response to clarification (Figures 4 and 7; not reproduced).

Table 70. Baseline characteristics included in estimation of weights for MAIC of entrectinib (efficacy sets) versus crizotinib (PROFILE 1001)

	Company efficacy set (n = 53)		ERG efficacy set (n = 78)		PROFILE 1001 crizotinib (n = 53)
Characteristic	**Entrectinib**	**Entrectinib re-weighted**	**Entrectinib**	**Entrectinib re-weighted**	
Effective sample size	[redacted]	[redacted]	[redacted]	[redacted]	53
% female	[redacted]	[redacted]	[redacted]	[redacted]	56.60
% Asian	[redacted]	[redacted]	[redacted]	[redacted]	39.62
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	1.89
% never smoker	[redacted]	[redacted]	[redacted]	[redacted]	75.47
% treatment naïve	[redacted]	[redacted]	[redacted]	[redacted]	13.21
Mean age	[redacted]	[redacted]	[redacted]	[redacted]	55

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, evidence review group; MAIC, matching adjusted indirect comparison. Data from CS Appendix D.1 Table 20 and response to clarification Table 18; Data reported for the ERG efficacy set were rounded to 1 decimal place but are considered to match the company's reweighted entrectinib population and the PEM+PLAT population.

The company use a wider entrectinib dataset including all patients with ROS1+ NSCLC regardless of measurable disease at baseline or prior ROS1-inhibitor therapy to conduct the MAICs for discontinuation due to AEs. A separate matching procedure was undertaken, and the characteristics shown in Table 71 shows that the wider study population was matched successfully to PROFILE 1001 for the chosen characteristics.

Table 71. Baseline characteristics included in estimation of weights for MAIC of entrectinib (safety set) versus crizotinib (PROFILE 1001)

	Entrectinib	Entrectinib re-weighted	PROFILE 1001 crizotinib (n = 53)
Characteristic			
Effective sample size	[redacted]	[redacted]	53
% female	[redacted]	[redacted]	56.60
% Asian	[redacted]	[redacted]	39.62
ECOG 2	[redacted]	[redacted]	1.89
% never smoker	[redacted]	[redacted]	75.47
% treatment naïve	[redacted]	[redacted]	13.21
Mean age	[redacted]	[redacted]	55

Abbreviations: AE, adverse events; ECOG, Eastern Cooperative Oncology Group; MAIC, matching adjusted indirect comparison. Data from CS Appendix D.1 Table 21.

The company also conducted an alternative MAIC to compare entrectinib with crizotinib using a population of 69 patients meeting STARTRK-2 eligibility criteria from the US Flatiron Health Analytic Database. The company acknowledge limitations in the Flatiron dataset due to missing baseline and outcome data and varying follow-up times. The ERG considered there to be insufficient information about the population and analysis presented to assess the robustness of the Flatiron MAIC and only discusses the results where large differences were noted between the results of the two analyses.

10.12.2 Matching procedure for entrectinib versus PEM+PLAT

For the comparison of entrectinib with ASCEND-4 PEM+PLAT with pemetrexed maintenance, the final baseline characteristics selected for matching were sex, race (Asian vs. non-Asian), ECOG (0 vs. 1 or 2), smoking history, age, and disease stage (stage IIIB vs stage IV non-CNS metastasis vs stage IV CNS metastasis). Histology was not included because it was not available for STARTRK-1 and, while the proportion of patients with adenocarcinoma in ASCEND-4 is [redacted] to the ERG's preferred efficacy set (93% and [redacted], respectively), the percentage with adenocarcinoma in the company's efficacy set is [redacted] ([redacted]).

Crucially, ASCEND-4 recruited a purely ALK+ population and there is no way to quantify, and if necessary adjust, for potential differences in treatment effect that are attributable to the underlying gene fusion (ALK+ or ROS1+). Furthermore, ASCEND-4 recruited a purely treatment-naïve population whereas most of the entrectinib-treated patients had received at least one prior therapy, which prevented matching on this basis.

Before reweighting, a higher proportion of entrectinib-treated patients had brain metastases ([redacted] and [redacted] depending on the choice of efficacy set versus 33.2% for PEM+PLAT) and ECOG performance status of 2 ([redacted] and [redacted] versus 5.88%), and a slightly lower proportion were never smokers ([redacted] and [redacted] versus 65.24%) than the PEM+PLAT arm of ASCEND-4. Full baseline characteristics before reweighting are provided in Appendix 10.2. Weighted patient characteristics for the company and ERG efficacy sets following the matching procedures show that the populations were matched successfully to the ASCEND-4 population for those chosen characteristics with a moderate reduction from sample size to effective sample size (Table 72). The distribution of weights and effective sample size for each variable was provided in the company's response to clarification (Figure 7).

Table 72. Baseline characteristics included in estimation of weights for MAIC of entrectinib (efficacy sets) versus PEM+PLAT (ASCEND-4)

	Company efficacy set (n = 53)		ERG efficacy set (n = 78)		PEM+PLAT with PEM maintenance
Characteristic	**Entrectinib**	**Entrectinib re-weighted**	**Entrectinib**	**Entrectinib re-weighted**	
Effective sample size	[redacted]	[redacted]	[redacted]	[redacted]	187
% female	[redacted]	[redacted]	[redacted]	[redacted]	60.96
% Asian	[redacted]	[redacted]	[redacted]	[redacted]	43.85
ECOG 2	[redacted]	[redacted]	[redacted]	[redacted]	5.88
% never smoker	[redacted]	[redacted]	[redacted]	[redacted]	65.24
Mean age	[redacted]	[redacted]	[redacted]	[redacted]	54
% stage III-B	[redacted]	[redacted]	[redacted]	[redacted]	2.67
% stage IV - CNS	[redacted]	[redacted]	[redacted]	[redacted]	33.16

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ERG, evidence review group; MAIC, matching adjusted indirect comparison; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.

Data from CS Appendix D.1 Table 22 and response to clarification Table 20. Data reported for the ERG efficacy set were rounded to 1 decimal place but are considered to match the company's reweighted entrectinib population and the PEM+PLAT population.

As for the crizotinib comparison, the company use a wider entrectinib dataset including all patients with ROS1+ NSCLC regardless of measurable disease at baseline or prior ROS1-inhibitor therapy to conduct the MAICs for discontinuation due to AEs. A separate matching procedure was undertaken, and the characteristics shown in Table 73 show that the wider study population was matched successfully to ASCEND-4 for the chosen characteristics.

Table 73. Baseline characteristics included in estimation of MAIC weights or comparison of entrectinib (safety set) versus PEM+PLAT (ASCEND-4)

Characteristic	Entrectinib	Entrectinib re-weighted	PEM+PLAT with PEM maintenance
Effective sample size	[redacted]	[redacted]	187
% female	[redacted]	[redacted]	61.0
% Asian	[redacted]	[redacted]	43.9
ECOG 2	[redacted]	[redacted]	5.9
% never smoker	[redacted]	[redacted]	65.2
Mean age	[redacted]	[redacted]	54
% stage III-B	[redacted]	[redacted]	2.7
% stage IV - CNS	[redacted]	[redacted]	33.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MAIC, matching adjusted indirect comparison; PEM+PLAT, pemetrexed plus platinum chemotherapy with pemetrexed maintenance.
Data from CS Appendix D.1 Table 23.

The method used to estimate PEM+PLAT in the economic model by applying HRs from PROFILE 1014 did not involve a matching procedure because it was not an MAIC.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report factual accuracy check – ERG response

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Issue 1 : EMA marketing authorisation date

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 14, 43 and 89 - The anticipated EMA marketing authorisation for entrectinib is noted as [redacted] - EMA marketing authorisation is anticipated in [redacted]	The anticipated marketing authorisation for entrectinib is as monotherapy for the treatment of patients with ROS1+, advanced NSCLC following confirmation of ROS1+ status, which is anticipated from the European Medicines Agency (EMA) in [redacted]	Incorrect data	The date stated in the ERG's report is in line with the date specified in Table 2 of the company's submission (CS). Pages 14, 43 and 89 have been amended to reflect the updated date provided by the company.

Issue 2 : Proportion of Asian patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 15, 65 and 90 - The proportion of Asian patients is reported as up to 47%, but should be 57% if based on single trial data or 36% if pooled. The company preference is to report	The proportion of Asian patients is higher in the entrectinib efficacy set than in the UK (36%), but race is not known to affect disease course or response to treatment in ROS1+ NSCLC	Incorrect data	'Up to 47%' refers to the proportion of patients who were Asian in the ERG's preferred efficacy set (46.2%; ERG report Table 55). The ERG has clarified on pages 15, 65 and 90 and

pooled data to align with the approach taken for other patient characteristic data reported in the paragraph.			corrected the transcription error (46.2 from 46.6%).
Page 58 - Proportion of Asian patients in the ERGs preferred efficacy set reported as 46.6% but should be 46.2%	Neither efficacy set is representative of the distribution of races in the UK population, but the ERG's efficacy set includes a smaller proportion of white patients (44.9% vs 58.5%) and a larger proportion of Asian patients (46.2% vs 35.8%) compared with the company's efficacy set; however, race is not known to affect disease course in ROS1+ NSCLC or response to treatment.	Minor data error	As above – the transcription error has been corrected to 46.2% on page 58, and updated from 47% to 46.2% on pages 15, 65 and 90.

Issue 3 : ASCEND-4 subsequent therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 18, 20, 73, 86 and 94 - when discussing the MAIC using ASCEND-4 it is noted that "at the time of analysis, 46% of patients who received PEM+PLAT had subsequently received crizotinib" - this was not reported in the company submission and cannot be verified in the primary source.	Please confirm data is correctly reported and provide reference, or amend to discussion of crossover as per the company submission where 43% of patients who received PEM+PLAT had subsequently received crizotinib	Unreferenced / potentially incorrect data	The ERG has corrected pages 18, 21, 73, 86 and 94 to read that, at the time of analysis, 80/187 (42.7%, not 46%) of patients who received PEM+PLAT in ASCEND-4 had crossed over to receive ceritinib (not crizotinib). The ERG has referenced Soria 2017 in all cases and added that 105/187 (51.6%) of patients who received PEM+PLAT in ASCEND-4 had subsequently received any ALK inhibitor (reported as 73% of those who

			had discontinued PEM+PLAT in Soria 2017).

Issue 4 : Real world survival data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 - real world survival reported as 51.5 months for crizotinib, should be 51.4 months	"Moreover, OS observed in studies of ROS1+ NSCLC, including those used for the MAICs, is much longer than has been achieved in clinical practice (51.5 months for crizotinib in PROFILE 1001 versus 18.5 months in the Flatiron registry), so the results may not reflect the effectiveness that might be expected for patients treated in the NHS"	Minor data error	Corrected to 51.4 months on pages 21, 78 and 162.

Issue 5 : Total cost of entrectinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 22, 32 157 and 163 - The total costs for entrectinib are reported to amount to [redacted]. With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (i.e. [redacted]). The total costs of entrectinib in the model are £[redacted], and would therefore need to be reduced by [redacted]	The total crizotinib costs in the ERG's preferred analysis amount to £118,912, while the total costs for entrectinib amount to [redacted]. With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (i.e. [redacted]). If the total costs associated with crizotinib were lower than [redacted] then the ICER for entrectinib vs crizotinib would increase as the total costs for crizotinib decrease.	Incorrect cost for entrectinib	The ERG has corrected the text (and values) as suggested by the company.

Issue 6 : Incorrect labelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 and 157 - Table C and Table 52: ERG's base case ICERs for entrectinib vs PEM+PLAT	Please correct the label in the table to "PEM + PLAT" rather than "crizotinib"	Incorrect label	Correction made on pages 32 and 157, and abbreviations added to footnotes

Issue 7 : Confidential markings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 - Figure 2 can be unmarked as per the revised marking in updated submission documents shared 21.06.19 Page 72 - Overall proportion of patients who received prior therapy can be unmarked as per the revised marking in updated submission documents shared 21.06.19	Removal of confidential marking on Figure 2 Removal of confidential marking on 'similar' note and 86.8% data	Minor marking-up error	Corrections made on pages 61 and 72. At the request of the technical team, raw mean utility values for PPS and PFS in STARTRK-2 have also been marked on pages 27, 28, 29, 31, 130, 132, 152, 153, 154 and 156.

Issue 8 : Formatting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 78 - please align formatting of censoring data across analysis sets; reported to no decimal places for company's analysis and one decimal place for ERG's	Censoring was required for 69.8% of the crizotinib group in the company's analysis and 49.1% of patients in the ERG's preferred analysis using the updated PROFILE 1001 data	Minor formatting inconsistency	Amended to 69.8% on pages 21, 78 and 162

preferred analysis. Company preference would be to stick to one decimal place throughout.			

Issue 9 : Comparative data for AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 83 and 88 - noted that comparative data for specific AEs used in the economic model are based on adjusted single-arm data for the company's or the ERG's preferred efficacy set but safety data not updated for the latter	Comparative data for specific AEs used in the economic model are based on unadjusted single-arm data for the company's efficacy set (n=53)	Misinterpretation	Text on pages 83 and 88 amended to reflect this.

Issue 10 : Cross-referencing issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 84, 126, 140, 141 and 143 - cross-reference error	Please re-insert cross-reference	Minor formatting error	Cross references updated
Page 105 -"This issue is further explored in Section 5.4.5.4 of the ERG report."	Please include section 5.4.5.4 or correct reference to correct section	Section 5.4.5.4 is missing	The sentence has been deleted.

Issue 11 : Incorrect text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 84 and 86 - Text presenting Figures 10-13 refer to comparison with crizotinib but figures and section are presenting comparison to PEM+PLAT	Please correct reference in text to comparison being presented: Figure 10 is a KM plot showing OS for entrectinib before and after reweighting compared with PEM + PLAT Figure 12 is a KM plot showing PFS for entrectinib before and after reweighting compared with PEM + PLAT	Incorrect comparator referenced	Corrections made to pages 84 and 86

Issue 12 : Figure titles

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85 - please include 'with pemetrexed maintenance' to the title of Figure 10 to align with Figure 11 and avoid any misinterpretation that different data are used across plots	Figure 10. KM plot of OS - company preferred MAIC versus PEM+PLAT with pemetrexed maintenance (ASCEND-4; reproduced from CS, Figure 9)	Minor formatting inconsistency	Figure 10 title amended as suggested

Issue 13 : Formatting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88 - Table 16 potentially missing footnote - asterix against median PFS but no linked footnote in table legend	Please add footnote or remove asterix	Minor formatting error	Asterisk has been removed

Page 94 – 'The company's MAIC based on PROFILE 1001' summary is presented twice in the final bullet point	Please remove the duplicated text	Minor formatting error	Duplication removed

Issue 14 : Incorrect figures

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115 & 116 - Table 20	It is not clear what assumptions have been made by the ERG to obtain the numbers in Table 20. The company assumes that the ERG are using their preferred dataset but not using the assumption of equal efficacy stated as the preferred assumption in the base case. As such, the numbers reported in table 20 do not match the ERGs model. Please correct the values for the ERGs preferred efficacy set: Entrectinib PFS to [redacted] (from [redacted]); Entrectinib OS to [redacted] (from [redacted]); Crizotinib PFS to 24.60 (from 23.60); Crizotinib OS to 43.08 (from 42.08); PEM+PLAT PROFILE1014 PFS to 11.69 (from 10.69); PEM+PLAT PROFILE1014 PFS to 15.57 (from 14.57); PEM+PLAT ASCEND-4 PFS to 11.43 (from 10.43); PEM+PLAT ASCEND-4 OS to 39.21 (from 38.21)	It is not clear what assumptions have been made by the ERG to obtain the numbers in table 20. The numbers reported in the table do not match the ERGs model.	Not a factual inaccuracy. The values reported in Table 20 of the ERG report are correct. The values are obtained when the switch in cell F234, tab "Model Inputs" is switched to "ERG preferred efficacy set". All other assumptions remain as in the company's base case. The results reported in Table 20 are the undiscounted mean months in PFS, PD and OS (for example, PFS for entrectinib is obtained by summing column AM13:AM1578 in the "Entrectinib_ROS1" tab).

Issue 15 : Formatting error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 120 and 121, Figures 26 and 27	The y axis of figures 26 and 27 are labelled as "progression-free survival" but figure 26 is showing ToT data, and figure 27 is showing PFS and ToT data.	Minor formatting error	The y axes have been relabeled in Figure 26 and 27 as suggested by the company and also in Figure 28.
Page 145 – Incorrect tables referenced - The company's PSA results (Table 46 and Table 47) are in line with the deterministic ones, with total costs and QALYs quite similar for both treatment comparisons in both analyses.	The company's PSA results (Table 44 and Table 45) are in line with the deterministic ones, with total costs and QALYs quite similar for both treatment comparisons in both analyses.	Minor formatting error	Text has been amended as suggested.

Issue 16 : Maintenance therapy cap

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 157: Table 52, scenario 10b where the ERG has applied a two-year cap to the drug costs for PEM+PLAT - patients still incur administration costs.	Please correct the error in the model and update results for this scenario	Minor error in model	Correction has been made and the relevant results updated.

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Addendum

This report was commissioned by the NIHR HTA Programme as project number 129317

BMJ Technology Assessment Group

Summary of the document

This addendum provides the Technology Appraisal Committee with the updated results from the economic model requested by NICE to be included in the technical engagement report. The NICE request was for the economic results containing the commercial access agreement (CAA) for pemetrexed; however, the ERG found a mistake in one of the company's scenario analyses in the model, while running the analysis. Therefore, the ERG produced this document, replicating the same results requested by NICE, with pemetrexed's list price. All the results provided include the entrectinib patient access scheme (PAS).

The document includes the results of the following analyses:

- Company's base case scenario;
- Company's base case scenario with errors corrected by the ERG and using the ERG's preferred efficacy set;
- ERG's base case ICER with different assumptions around the duration of maintenance therapy with pemetrexed and ROS1 testing costs.

The results are reported in tabular format, replicating the tables included in the ERG report.

COMPANY'S BASE CASE

Table 2. Company's base case results with PAS included for entrectinib vs PEM+PLAT (Table 40, ERG report)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,930	1.51	1.01	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,628

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 3. Company's base case results with PAS included for entrectinib vs crizotinib (Table 41, ERG report)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	137,637	4.35	2.63	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

COMPANY'S BASE CASE ANALYSIS CORRECTED BY THE ERG

Table 4. Company's base case results with PAS included for entrectinib vs PEM+PLAT (with corrections) for ERG's preferred analysis set (Table 48, ERG report)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pemetrexed plus platinum	£20,470	1.28	0.87	–	–	–	–
Entrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,845

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 4. Company's base case results with PAS included for entrectinib vs crizotinib (with corrections) for ERG's preferred analysis set (Table 49, ERG report)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Entrectinib	[redacted]	[redacted]	[redacted]	–	–	–	–
Crizotinib	£128,926	3.54	2.22	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

ADDITIONAL WORK UNDERTAKEN BY THE ERG

ERG's alternative base case ICERs

The final cumulative ICER for entrectinib vs PEM+PLAT is highly dependent on the assumption made for duration of maintenance treatment with pemetrexed. The ERG's cumulative base case ICER assuming a 2-year cap on maintenance treatment (all changes listed in Table 4 including 3+4+a+6+7+8+11+10b) amounts to £31,190 per QALY gained (£26,014 if the cost of ROS1 testing is excluded from the analysis).

If maintenance treatment is assumed to be given for 6 cycles (as the ERG's clinical experts indicated this is a clinically plausible median duration), the ERG's cumulative base case ICER (all changes listed in Table 4 including 3+4+a+6+7+8+11+d) is £43,880 per QALY gained (£38,704 if the cost of ROS1 testing is excluded from the analysis).

Assuming 8 cycles of maintenance treatment in the ERG's base case model results in a £41,905 (all changes listed in Table 4 including 3+4+a+6+7+8+11+c) per QALY gained (£36,728 if the cost of ROS1 testing is excluded from the analysis). The ERG notes that this ICER corresponds with aligning the treatment effectiveness of PEM+PLAT in the ERG's base case with the respective costs in the underlying ASCEND-4 study.

Table 4. ERG's base case ICERs for entrectinib vs PEM+PLAT (ERG report, Table 52 adapted)

Analysis from list	Results per patient	Entrectinib (1)	PEM+PLAT (2)	Incremental value (1-2)
0	**Company's corrected base using ERG's preferred efficacy set**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,845**	
3+4	**Assuming a PFS and OS HR=1 for entrectinib vs crizotinib**			
	Total costs (£)	[redacted]	21,493	[redacted]
	QALYs	[redacted]	1.09	[redacted]
	ICER		**£24,083**	
a	**Using the TA529-accepted utility values of of 0.81 for PFS and 0.66 for PPS**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.95	[redacted]
	ICER		**£21,232**	
6	**Assuming that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments**			
	Total costs (£)	[redacted]	21,662	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER		**£21,796**	
7	**Using the ERG's clinical expert's suggested resource for the PFS and PPS sates**			

	Total costs (£)	[redacted]	21,299	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER	**£22,812**		
8	**Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib or crizotinib**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER	**£26,010**		
11	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of induction treatment with PEM from 6 to 4 cycles to match the duration of induction treatment with PEM in ASCEND-4**			
	Total costs (£)	[redacted]	21,095	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER	**£52,399**		
10b	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of induction treatment with PEM from 6 to 4 cycles to match the duration of induction treatment with PEM in ASCEND-4 (given with cisplatin or carboplatin) and assuming maintenance treatment after cisplatin and carboplatin until patients progress (for a maximum of 2 years)**			
	Total costs (£)	[redacted]	39,506	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER	**£28,438**		
b	**Removing the costs of testing for ROS1**			
	Total costs (£)	[redacted]	20,470	[redacted]
	QALYs	[redacted]	0.87	[redacted]
	ICER	**£19,566**		
c	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of induction treatment with PEM from 6 to 4 cycles to match the duration of induction treatment with PEM in ASCEND-4 (given with cisplatin or carboplatin) + assuming 8 cycles of maintenance with PEM alone**			
	Total costs (£)	[redacted]	30,677	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER	**£39,928**		
d	**Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of induction treatment with PEM from 6 to 4 cycles to match the duration of induction treatment with PEM in ASCEND-4 (given with cisplatin or carboplatin) + assuming 6 cycles of maintenance with PEM alone**			
	Total costs (£)	[redacted]	29,050	[redacted]
	QALYs	[redacted]	1.98	[redacted]
	ICER	**£42,046**		

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

The total crizotinib costs in the ERG's base case amounts to £125,425 (£121,160 without the cost of ROS1 testing) while the total costs for entrectinib amounts to [redacted] without the cost of ROS1 testing). With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to

yield the same total cost in the economic analysis as entrectinib (both with and without the test of ROS1 testing).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1541]

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

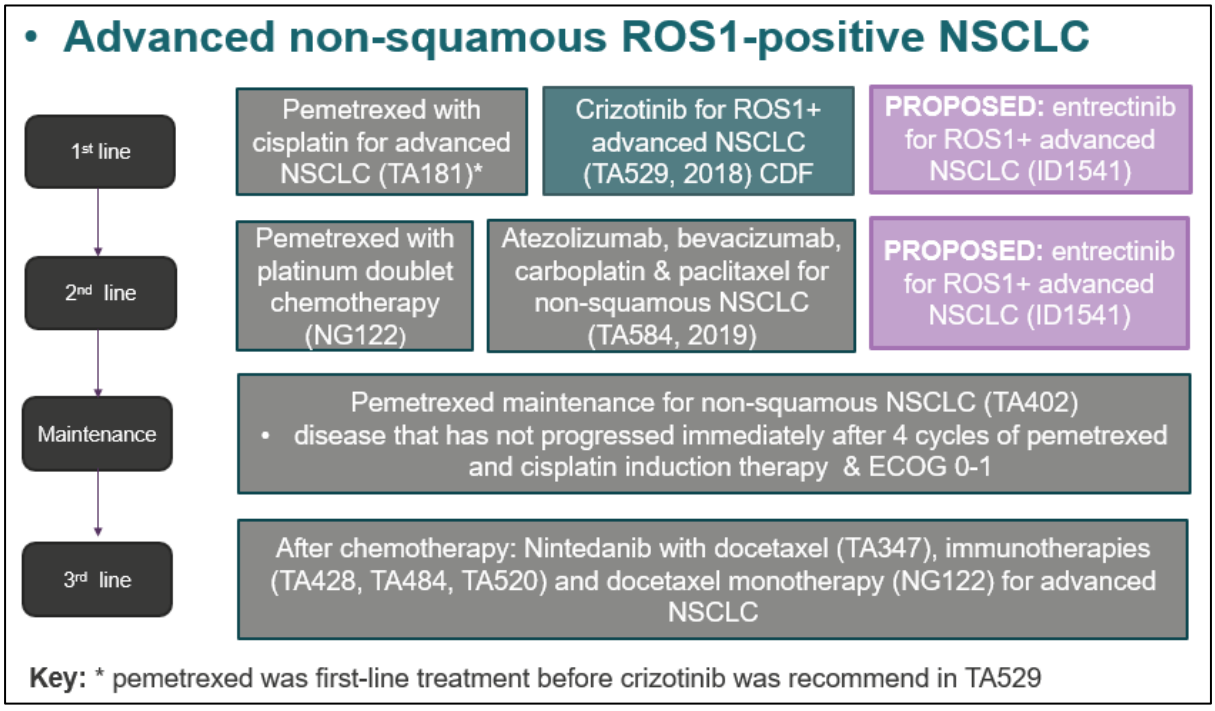
Issue date: September 2019

1. Topic background

1.1 Disease background: NSCLC

- Lung cancer is third most common cancer in the UK (~13% of all cancer).
- Most (~ 88%) lung cancers are non-small cell lung cancer (NSCLC).
- NSCLC can be squamous - squamous cell carcinoma or non-squamous - adenocarcinoma (most non-squamous cancers) and large-cell carcinoma.
- In 2016 approximately 32,533 people were diagnosed with NSCLC in England, of whom 53% had stage IV disease.
- Prognosis is often poor due to late diagnosis.
- Central nervous system (CNS) metastasis are common in advanced NSCLC.
- ROS1 is a rare mutation that occurs in around 1-2% of NSCLC, mostly in non-squamous tumours, with the majority in adenocarcinoma (80-100%).
- ROS1 testing is a standard part of the diagnostic work-up in NSCLC.
- Similarly to ALK mutations, ROS1 mutations are more common in younger people who have never smoked and have adenocarcinoma and were associated with worse prognosis.

1.2 Treatment pathway



1.3 Clinical evidence: key trials

Study	ALKA-372-001: ALKA	RXDX-101-01: STARTRK-1	RXDX-101-02: STARTRK-2
Study design	ongoing, Phase I, single-arm, open-label, ascending-dose study	ongoing, Phase I, single-arm, open-label, ascending-dose study	ongoing, Phase II, global, single-arm, multicentre, basket study
Population	≥18 years old with advanced or metastatic solid tumours with TRKA/B/C, ROS1, or ALK molecular alterations	≥18 years old with solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations	≥18 years old with advanced or metastatic solid tumours with NTRK1/2/3, ROS1, or ALK gene fusion (excluding ALK-positive NSCLC)
Location	Italy	US, South Korea and Spain	Australia, Europe (inc. UK), Asia & North America (US)
Intervention	Entrectinib (n=58)	Entrectinib (n=76)	Entrectinib (n=207)
Comparator	N/A	N/A	N/A
Supports MA	Yes	Yes	Yes
Used in model	**Company:** included people with measurable disease at baseline, any entrectinib dosing and ≥12 months follow-up: ALKA (n=9), STARTRK-1 (n=7) & STARTRK-2 (n=37) and pooled evidence across (n=53). **ERG:** included people with measurable disease at baseline who received 600mg entrectinib, irrespective of follow-up duration: subgroup of STARTRK-2 (n=78).		

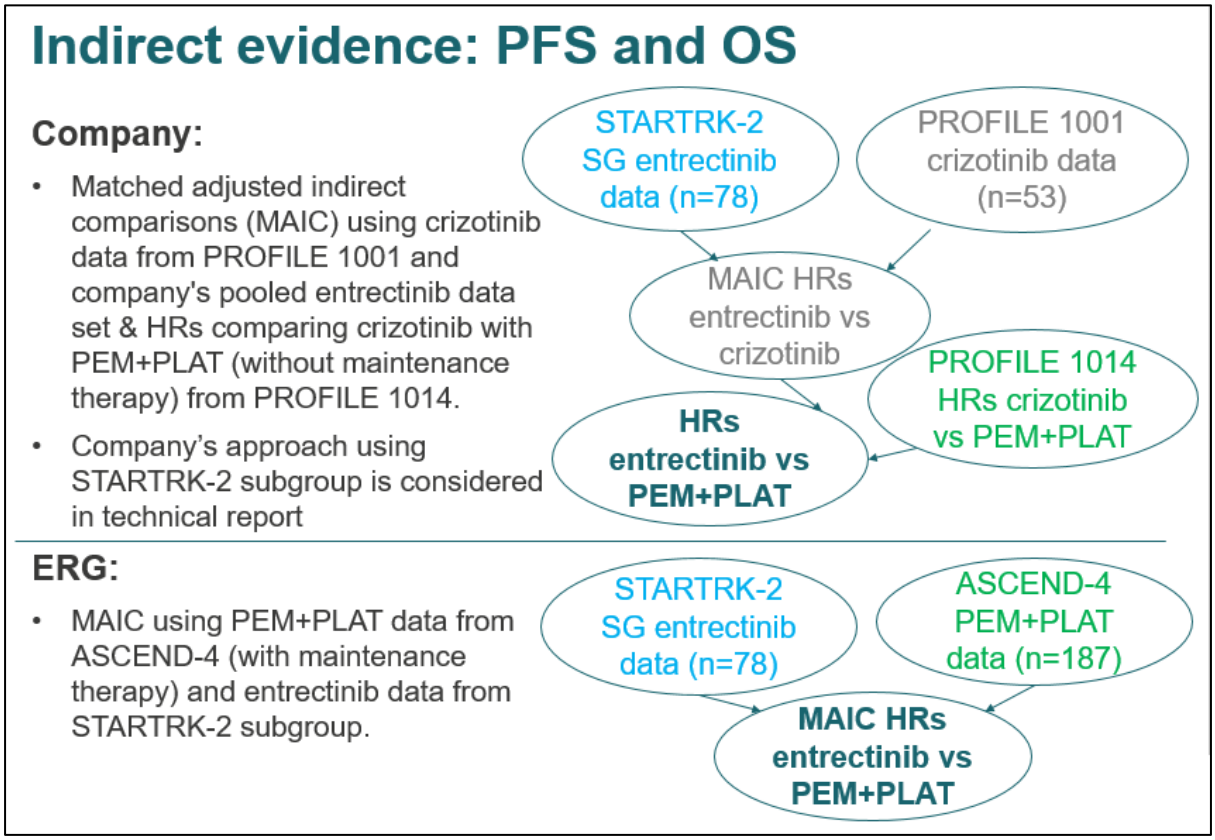
1.4 Clinical evidence: baseline characteristic

		Company's pooled subgroup (n=53)	ERG's STARTRK-2 subgroup (n=78)
Age, years (mean)		53.5 years	53.3 years
Female, n (%)		34 (64%)	49 (63%)
ECOG, n (%)	• 0 • 1 • 2	• 20 (38%) • 27 (51%) • 6 (11%)	• 30 (39%) • 38 (49%) • 10 (12%)
Histology	• adenocarcinoma • bronchioloalveolar carcinoma • other carcinoma • cytological • histological	• 35 (76%) • 1 (2%) • 1 (1%) • 2 (4%) • 7 (15%)	• 76 (98%) • 1 (1%) • 1 (1%) • - • -
Time from diagnosis, months (mean)		21.0 months	20.7 months
Metastatic vs. locally advanced disease, n (%)		50 (94%) vs 2 (4%) vs 1 (2%) with localised disease	77 (99%) vs 1 (1%)
Baseline CNS lesions, n (%)	• Absent • Present: not measurable + measurable	• 30 (57% • 18 (34%) + 5 (9%)	• 43 (55%) • 27 (35%) + 8 (10%)

1.5 Clinical evidence: key trial results

31 May 2018 patient enrolment data cut-off		Company's pooled analysis (n=53)	ERG's STARTRK-2 subgroup (n=78)
OS	Patients, n (%)	[redacted]	[redacted]
	median (95%CI), months	[redacted]	[redacted]
PFS	Patients, n (%)	[redacted]	[redacted]
	median (95%CI), months	[redacted]	[redacted]
CNS PFS	Patients, n (%)	[redacted]	[redacted]
	median (95%CI), months	[redacted]	[redacted]
OR	Patients with OR, n (%)	[redacted]	[redacted]
	95% CI for rate	[redacted]	[redacted]
	median duration (95%CI), months	[redacted]	[redacted]

1.6 Clinical evidence: indirect evidence



1.7 Clinical evidence: indirect evidence results

		Sample Size	Number of events	Median time to event, Months (95% CI)	HR vs comparator (95% CI)
ERG's approach: MAIC using STARTRK-2 SG (n=78) and PEM+PLAT data (n=187) from ASCEND-4 to estimate PEM+PLAT					
OS	Entrectinib MAIC	[redacted]	[redacted]	[redacted]	[redacted]
	Entrectinib unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	Pemetrexed regimen	187	59/86*	26.26 (22.84, NE)	-
PFS	Entrectinib MAIC	[redacted]	[redacted]	[redacted]	[redacted]
	Entrectinib unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	Pemetrexed regimen	187	117	7.99 (5.70, 11.13)	-
Company's approach: MAIC using STARTRK-2 SG (n=78) and crizotinib PROFILE 1001 data (53) and HR from PROFILE 1014 to estimate PEM+PLAT					
OS	Entrectinib MAIC	[redacted]	[redacted]	[redacted]	[redacted]
	Entrectinib unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	Crizotinib	53	27	51.5 (30.37, NE)	-
	HR of crizotinib vs pemetrexed from PROFILE 1014				0.346 (0.081, 0.718)
PFS	Entrectinib MAIC	[redacted]	[redacted]	[redacted]	[redacted]
	Entrectinib unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
	Crizotinib	53	36	19.33 (15.27, 40.37)	-
	HR of crizotinib vs pemetrexed from PROFILE 1014				0.45 (0.35, 0.60)

Key: * both values reported in company's submission

= HRs used in the model by ERG

= HRs used in the model by company

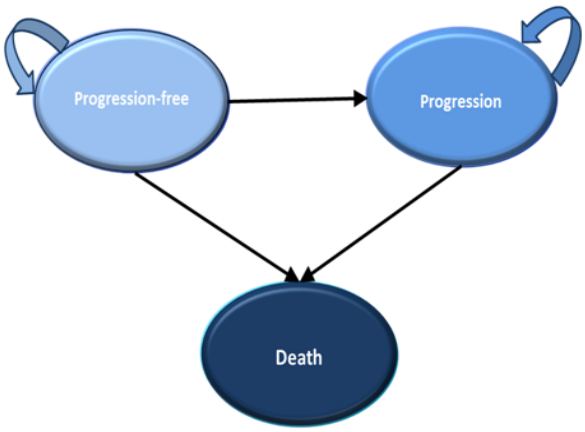
1.8 Model structure

Company's model

- Cohort based partitioned survival model with 3 states:

  Progression-free, Progressed disease and *Death*

- Similar to model used in TA529
- 30-day cycle length, with a half-cycle correction applied
- time horizon of 30 years.
- NHS and Personal Social Services (PSS) perspective
- Costs and health effects are discounted at an annual rate of 3.5%



1.9 Modelled PFS and OS

PFS, PPS and OS (undiscounted) using STARTRK-2 subgroup (n=78)

Time, months	Entrectinib	ERG's approach		company's approach	
		PEM+PLAT	Entrectinib gain	PEM+PLAT	Entrectinib gain
Mean OS	[redacted]	39.21	[redacted]	15.57	[redacted]
Median OS	[redacted]	26.6	[redacted]	10.8	[redacted]
Mean PFS	[redacted]	11.43	[redacted]	11.69	[redacted]
Median PFS	[redacted]	7.9	[redacted]	7.9	[redacted]
Mean PPS	[redacted]	27.78	[redacted]	3.87	[redacted]
Median PPS	[redacted]	18.7	[redacted]	2.9	[redacted]

Percentage of patients alive using STARTRK-2 subgroup (n=78)

Years	Entrectinib	PEM+PLAT ERG's approach	PEM+PLAT company's approach
2.0	[redacted]	54.1%	19.9%
4.0	[redacted]	28.1%	3.6%
5.0	[redacted]	20.5%	1.6%
10.0	[redacted]	4.2%	0.0%
15.0	[redacted]	0.8%	0.0%
30.0	[redacted]	0.0%	0.0%

1.10 Quality-adjusted life years and life years by heath-state in ERG's preferred base case

Mean (95%CI)		Entrectinib	PEM+PLAT	Incremental QALY/LY
QALY	PFS	[redacted]	0.74	[redacted]
	Progression	[redacted]	1.31	[redacted]
	total	[redacted]	2.05	[redacted]
LY	PFS	[redacted]	0.913	[redacted]
	Progression	[redacted]	1.998	[redacted]
	Total	[redacted]	2.91	[redacted]

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Pemetrexed with platinum drug (PEM+PLAT) is the key comparator in this appraisal. In line with the NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not a comparator in this appraisal. The company proposes that entrectinib will be used at first or second line for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC).

Issue 2 The company's primary efficacy set is based on 53 patients from 2 Phase I studies (ALKA and STARTRK-1) and 1 Phase II study (STARTRK-2) who had:

- confirmed diagnosis of ROS1-positive NSCLC;
- measurable disease at baseline;
- at least 12 months' follow-up from the time of first response;
- unlicensed doses (100 mg/m^2 to 1600 mg/m^2); and
- no prior ROS1 inhibitor treatment.

The ERG's preferred dataset was a STARTRK-2 subgroup of 78 patients who had:

- confirmed diagnosis of ROS1-positive NSCLC;
- measurable disease at baseline;
- no minimum follow-up restriction;
- received the licensed 600 mg entrectinib dose; and
- no prior ROS1 inhibitor treatment.

The technical team considered the STARTRK-2 subgroup to be in line with the marketing authorisation for entrectinib and therefore more representative of NHS clinical practice while also being a larger and more robust data set. The technical report focuses on the company's and ERG's analyses using the STARTRK-2 subgroup (n=78).

Issue 3 STARTRK-2, the key clinical trial is a single arm phase II basket trial. In order to compare entrectinib with PEM+PLAT, a matching adjusted indirect comparison (MAIC) was conducted using data from ASCEND-4 trial in ALK-positive NSCLC. The technical team considers the results of the MAIC to be appropriate for decision making. However, it is concerned with the high level of uncertainty of the resulting progression free survival (PFS) and overall survival (OS) estimates due to using evidence from ALK-positive NSCLC and due to differences in prior and subsequent treatments used in the ASCEND-4 and STARTRK-2 trials. It is not possible to estimate the direction or size of the effect the uncertainty has on the MAIC results.

Issue 4 To estimate PEM+PLAT, the company estimated the crizotinib curve first by using HRs from PROFILE 1001 MAIC, and then applied HR from PROFILE 1014 comparing crizotinib with PEM+PLAT (without pemetrexed maintenance therapy) to the crizotinib curve. The technical team considers the ERG's approach estimating PEM+PLAT using HRs from the ASCEND-4 MAIC more suitable as it does not require estimating the crizotinib curve first, because of the uncertainty around the OS HR from PROFILE 1014 due to high level of cross-over, and because ASCEND-4 trial used maintenance therapy. However, it notes that, although entrectinib survival gains seems to be clinically plausible, the modelled mean survival of 39.21 months with PEM+PLAT seems to be very high. It therefore considers the results highly uncertain.

Issue 5 It has been accepted that the life expectancy of patients treated with PEM+PLAT is less than 24 months in a recent appraisal in ROS1-positive NSCLC (TA529). Although the model in this case predicts that survival with PEM+PLAT is longer than 24 months, the technical team considers, that based on precedence, entrectinib is likely to meet both criteria to be considered a life-

extending, end-of-life treatment when compared with PEM+PLAT.

Issue 6 The company modelled pemetrexed maintenance therapy only after pemetrexed with cisplatin in line with TA402 and in its base case they assumed no maintenance therapy. In the ASCEND-4 trial used to estimate PEM+PLAT in the model, pemetrexed maintenance therapy was used for approximately 8 cycles. To reflect current clinical practice and to align the clinical evidence with ASCEND-4, the technical team assumed that pemetrexed maintenance therapy is given for 8 cycles after an induction treatment with pemetrexed with either cisplatin or carboplatin.

Issue 7 The company assumed a range of subsequent treatments in its model, and only some patients ([redacted] in the STARTRK-2 subgroup) received subsequent treatments. The cost of subsequent treatments was applied as one-off cost in the model. To reflect UK clinical practice, the technical team assumed:

- 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments.
- PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib.

However, this approach is not based on the underlying clinical data and includes only second-line subsequent treatments costs.

Issue 8 The company estimated PFS utility from STARTRK-2 (0.73), however it used utility value from TA529 for post progression survival (PPS; 0.66). Given that only one set of utility data comes from the trial and that the regression model hasn't been implemented correctly, the technical team considers using the same utilities as used in TA529, 0.81 for PFS and 0.66 for PPS to be more appropriate.

Issue 9 The company based its health costs on previous appraisals. However, some of the assumptions related to the resource use for disease management were not considered to be fully reflective of UK clinical practice and alternative values as proposed by ERG's clinical experts were used instead.

Issue 10 The company is actively seeking a Cancer Drugs Fund (CDF) recommendation for entrectinib. The technical team considers that entrectinib meets the criteria for inclusion in the Cancer Drugs Fund.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and cannot be resolved (see table 2):

- The clinical trial evidence is based on a small subgroup (n=78) from a single arm trial.
- Because of the small size of the clinical evidence, it was not possible to differentiate between naïve and previously treated patients and so an "all-lines" approach has been used.
- The clinical trial evidence is immature; median overall survival has not been met.
- No direct comparative evidence, and no indirect comparative evidence in ROS1-positive advanced NSCLC is available. Indirect comparison with PEM+PLAT has been drawn using data from ALK-positive NSCLC in ASCEND-4 trial (see issue 3).
- Comparative data for specific adverse events used in the economic model are based on unadjusted data from the company's preferred efficacy set for entrectinib (n = 53) and the PEM+PLAT arm of PROFILE 1014 trial (n = 171).

- No data for PEM+PLAT induction treatment duration is available. The company assumed 6 cycles in its base case and the ERG and technical team assumed 4 cycles.

2.3 The cost-effectiveness results presented in the company submission and ERG report included ROS1-testing costs. ROS1 testing is now considered to be routine practice for NSCLC and therefore the costs of ROS1-testing were removed from all cost-effectiveness results (table 3).

2.4 The cost-effectiveness results include a proposed patient access scheme (PAS) for entrectinib, however a discount for pemetrexed maintenance therapy is not included because it is confidential. Results including all confidential discounts will be discussed by the committee.

2.5 Taking these aspects into account, the resulting incremental cost-effectiveness ratio (ICER) of entrectinib (with PAS applied) compared with PEM+PLAT is £28,824 per QALY gained (see table 1). However, the most plausible ICER for entrectinib can be higher or lower that £28,824 per QALY gained, because of the high level of uncertainly around its calculation. The ICER is based on an extrapolation of an indirect comparison combining data for entrectinib in ROS1-positive NSCLC with data from a trial comparing PEM+PLAT with ceritinib in ALK-positive NSCLC and is therefore highly uncertain. In addition, the ICER is sensitive to the assumption around the duration of maintenance treatment with pemetrexed. If maintenance treatment is assumed to be given for 6 cycles, the ICER increases to £30,799 per QALY gained and when maintenance treatment is assumed until patients progress (for a maximum of 2 years), it decreases to £18,109 per QALY gained. Table 3 below includes other issues for information some of which introduce additional uncertainty to the cost-effectiveness estimates provided.

2.6 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Comparators

Questions for engagement	1. Is pemetrexed in combination with a platinum drug (PEM+PLAT) the key comparator in this appraisal? In line with NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not considered a comparator in the appraisal.
Background/description of issue	In line with NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not a comparator in this appraisal: *Treatments that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice because:* • *Regulation 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 does not apply at this point.* • *Their use is not embedded in clinical practice because no further funding will be available for patients to be prescribed the drug if NICE does not recommend the drug for routine commissioning at the end of the managed access period.* • *Although they have plausible potential to satisfy the criteria for routine commissioning, the uncertainty in the clinical data (and consequently the cost-effectiveness estimates) was too great to make such a recommendation at the time of the appraisal.* The final scope listed the following comparators: Untreated disease: • chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only)

	o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy After previous chemotherapy treatments: • docetaxel, with (for adenocarcinoma histology) or without nintedanib Entrectinib is an oral, potent inhibitor of the tyrosine kinases encoded by the ROS1, NTRK1, NTRK2, NTRK3 and ALK genes with activity in the central nervous system (CNS). The anticipated marketing authorisation for entrectinib [redacted]. Section 1.2 summarises the available treatments for advanced ROS1-positive NSCLC. The clinical pathway for advanced ROS1-positive NSCLC has changed: • ROS1 testing was included in the 2019/2020 National Genomic Test Directory and is a standard part of diagnostic work-up in NSCLC. • crizotinib, ROS1-targeted therapy, was recommended via the Cancer Drugs Fund (CDF) in 2018 for treating ROS1-positive advanced NSCLC in adults (TA529) and has become first-line treatment of choice for ROS1-positive advanced NSCLC. • prior to crizotinib funding through the CDF, PEM+PLAT was considered the standard of care for ROS1-positive NSCLC patients (TA181). PEM+PLAT is now being used in the second-line setting. • pemetrexed maintenance therapy is given after initial treatment with pemetrexed in combination with either cisplatin or carboplatin (see issue 6 for more information). • atezolizumab plus bevacizumab, carboplatin and paclitaxel was recommended in June 2019 as an option for some people with metastatic NSCLC (TA584) including is a second-line treatment for some ROS1-positive NSCLC. **The company** (B.1.3.) proposes that entrectinib will be used at first or second line for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC). The company (section B.3.7) presented a comparison with PEM+PLAT in its base case. However, they considered crizotinib to be the preferred first-line treatment and [redacted]

	[redacted]. The company therefore included a comparison with crizotinib in a scenario analysis. They considered crizotinib to be a relevant first-line comparator and PEM+PLAT to be a second-line comparator. **The ERG** agreed with the company's choice of comparators and explained that the remaining comparators listed in the NICE final scope are not relevant because they are all used later in the pathway after crizotinib and PEM+PLAT, whereas entrectinib would be used as an alternative to first- and second-line treatments. The ERG's clinical experts noted that entrectinib is likely to displace crizotinib as the preferred first-line treatment should it be recommended because of its anticipated benefits for treating and preventing CNS disease.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of entrectinib, it is important to establish the relevant comparators.
Technical team preliminary judgement and rationale	**The technical team** considers PEM+PLAT to be the key comparator in this appraisal. PEM+PLAT is currently used as a second-line treatment and was used as a first-line treatment before crizotinib was available via CDF. All other treatments are used later in the pathway or recommended via CDF and are therefore not considered to be relevant comparators.

Issue 2 – Population

Questions for engagement	2. Is the ERG's STARTRK-2 subgroup (n=78) or the company's analysis set (n=53) more appropriate for decision making?
Background/description of issue	**The company's clinical evidence** (section B.2.3.) is based on 53 patients from 2 Phase I studies (ALKA; n = 58; Italy, and STARTRK-1; n = 76; USA, South Korea and Spain) and 1 Phase II study (STARTRK-2; n = 207; Australia, Europe, Asia and the USA). The company highlights that their integrated analysis was prespecified in agreement with the FDA. The integrated analysis included patients who had: • A confirmed diagnosis of ROS1-positive NSCLC; • measurable disease at baseline; • at least 12 months' follow-up from the time of first response; • unlicensed doses (100 mg/m2 to 1600 mg/m2); and • no prior ROS1 inhibitor treatment. **The ERG** noted that the company excluded [redacted] patients who had less than 12 months' follow-up and that ALKA and STARTRK-1 trials included people with entrectinib doses and schedules outside the intended marketing authorisation of 600 mg once daily. The ERG was concerned that the minimum follow-up restriction introduced selection bias. It explained that patients with no events during shorter follow-ups contribute useful information for key survival outcomes (OS and PFS) through censoring. At the clarification stage, the company confirmed that the EMA [redacted]. The ERG's preferred analysis was therefore based on a subgroup of 78 patients from STARTRK-2 who had: • a confirmed diagnosis of ROS1opositive NSCLC; • measurable disease at baseline; • no minimum follow-up restriction;

	• received the 600 mg entrectinib licence dose; • no prior ROS1 inhibitor treatment. Sections 1.3 to 1.5 summarise the available clinical evidence. In the STARTRK-2 subgroup, 57 patients (73.1%) received one or more systemic treatments before entrectinib, leaving only 21 treatment-naïve patients (i.e. not having received prior systemic therapies). Similarly, the company's pooled subgroup had 36 patients (67.9%) with prior systemic treatment and only 17 treatment-naïve patients. Therefore, the available evidence is a more accurate representation of patients treated in second line rather than first line. The company explained (section B.3.2.) that given the small size of the key clinical trials, it was not possible to differentiate between naïve and previously treated patients and so an "all-lines" approach has been used in order to maximise the patient numbers and robustness of the available data. ERG's clinical experts explained that it would have been impractical to run a first line trial for rare cancer subtypes. As a result, the treatment effects based on the largely pre-treated population who received entrectinib may underestimate the potential benefit of entrectinib for patients with untreated ROS1-positive NSCLC. However, they noted that the impact of prior treatments on the assessment of entrectinib effectiveness at first line is mitigated by the exclusion of patients who had received prior ROS1 inhibitors, which would have the biggest impact on the benefits of entrectinib. While prior chemotherapy treatments are not expected to have a major impact on effectiveness, the impact of other targeted therapies and immunotherapies is unknown.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of entrectinib, it is important to establish what population is the most relevant to this appraisal.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG, that the STARTRK-2 subgroup (n=78) is more representative of NHS clinical practice while also being a larger and more robust data set. The technical report focuses on the analyses using the STARTRK-2 subgroup (n=78).

Issue 3 – Indirect comparison entrectinib versus pemetrexed

Questions for engagement	3a. Do you consider the use of evidence for the comparator PEM+PLAT from ALK-positive populations as a proxy for ROS1-positive NSCLC appropriate in the absence of ROS1-positive evidence? 3b. Do you consider the result of the indirect comparison of entrectinib with PEM+PLAT to be clinically plausible (figures 1 & 2 and tables A & B in Issue 4)?
Background/description of issue	STARTRK-2, an ongoing single arm phase II basket trial (Australia, Europe, Asia and the USA), recruited adults with advanced or metastatic solid tumours with NTRK, ROS1, or ALK gene alterations (excluding ALK NSCLC). It has so far recruited 207 patients. It enrolled [redacted] patients with ROS1-positive NSCLC. After excluding people with prior ROS1-targeted therapy ([redacted]) and for other reasons ([redacted]), the ROS1-positive NSCLC STARTK-2 efficacy set has [redacted] patients. The preferred STARTRK-2 subgroup includes 78 patients as it further excluded [redacted] people who did not have measurable disease at baseline (<12 months follow-up). See sections 1.3 to 1.5 for details of the trial and the STARTRK-2 preferred subgroup. **The company** (section B.2.9.) conducted systematic reviews to conduct an indirect comparison with PEM+PLAT. No studies with ROS1-positive patients were identified, so the company broaden the search and identified 9 studies in locally advanced or metastatic anaplastic lymphoma kinase-positive (ALK-positive) NSCLC (see Table 58 in ERG report for details). ASCEND-4 was considered

the most appropriate because it is the only study to have given pemetrexed maintenance therapy, which most patients receive after PEM+PLAT therapy in UK clinical practice.

ASCEND-4, a large, multicentre, Phase III RCT of ceritinib versus PEM+PLAT (with pemetrexed maintenance therapy) for untreated ALK-positive NSCLC, recruited 375 participants.

Matching adjusted indirect comparison (MAIC) was conducted using:

- PEM+PLAT data from the ASCEND-4 trial in ALK-positive NSCLC, and
- STARTRK-2 subgroup.

Results are presented in figure 1 & 2.

The MAIC results suggest [redacted] of entrectinib versus PEM+PLAT for OS (HR [redacted] 95% CI: [redacted]). The KM plot suggests [redacted] (figure 1).

Figure 1. KM plot of OS

Source: ERG figure 11

	The MAIC results show [redacted] of entrectinib versus PEM+PLAT for PFS (HR [redacted] 95% CI: [redacted]). The KM plot shows that reweighting [redacted] the difference between treatments (figure 2). [redacted] **Figure 2. KM plot of PFS** Source: ERG figure 13 The ERG considered that the choice of ASCEND-4 for the MAIC was not justified fully, however was unable to investigate alternatives within the time available. Nevertheless, the ERG considered

	ASCEND-4 to be a well conducted RCT and agreed with the company that ASCEND-4 was the only study to give pemetrexed maintenance therapy as is done in UK clinical practice. They noted: • patients receiving PEM+PLAT in ASCEND-4 were previously untreated, and 42.7% had subsequently received ceritinib (and 51.6% received an ALK inhibitor). As a result, the survival benefit of entrectinib versus PEM+PLAT as a second-line therapy is likely to be underestimated. Regarding the use of ALK-positive population as a proxy for ROS1-positive NSCLC they explained: • There is no consensus regarding the use of evidence from ALK-positive populations as a proxy for ROS1-positive NSCLC, and there is no way to quantify and, if necessary, adjust for differences in treatment effects that are attributable to the underlying gene fusion. • The two populations are demographically similar (younger age than NSCLC in general, higher proportion of non-smokers, primarily adenocarcinoma histology), treatments are comparable, and the kinases of ROS1 and ALK share 77% of amino acids. • PFS was longer with crizotinib in PROFILE 1001 (ROS1-positive NSCLC) than in PROFILE 1014 and PROFILE 1007 (ALK-positive NSCLC), but ROS1 fusions are rare and naïve comparisons may be confounded by baseline differences and prior treatments. • The appraisal committee for TA529 considered the use of evidence from patients with ALK-positive NSCLC, "very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals".
Why this issue is important	It is important to establish the clinical effectiveness of entrectinib compared with PEM+PLAT to be able to estimate the cost-effectiveness of entrectinib compared with PEM+PLAT.
Technical team preliminary judgement and rationale	The technical team considers the results of MAIC from ASCEND-4 to be appropriate for decision making. However, it is concern with the high level of uncertainty of the PFS and OS estimates due to: • using evidence from ALK-positive NSCLC, and • differences in prior and subsequent treatments used ASCEND-4 and STARTRK-2. Further, it is concern that it is not possible to estimate the direction or size of the effect the uncertainty has on the MAIC results.

Issue 4 – OS and PFS modelling

Questions for engagement	4. What approach to estimating PEM+PLAT overall survival (OS) and progression free survival (PFS) is appropriate for decision making (figure 3 & 4)? • ERG's preferred approach: hazard ratios (HRs) from an indirect comparison of entrectinib with PEM+PLAT using data from ASCEND-4 (with maintenance therapy) to estimate PEM+PLAT curve. • Company's preferred approach: HRs from an indirect comparison of entrectinib with crizotinib using data from PROFILE 1001, and applying HRs comparing crizotinib with PEM+PLAT (without maintenance therapy) from PROFILE 1014 to the estimated crizotinib curve to model PEM+PLAT.
Background/description of issue	Overall survival (OS) and progression free survival (PFS) for the entrectinib arm were estimated using the ROS1-positive data from the ERG's STARTRK-2 subgroup (n=78). • All standard parametric models were considered and compared, and the company chose exponential model as the most suitable. The ERG considered the exponential models to be a reasonable fit for PFS and OS. But noted that as comparators are estimated using HRs applied to the entrectinib curve, all curves in the model are based on exponential distributions and as such assume constant hazards. • The company used two approaches (details below). The ERG explained that both approaches presented by the company to estimate OS for PEM+PLAT have considerable flaws. However, it considered that using the ASCEND-4 MAIC produces more conservative results and therefore included this approach in its preferred base case. Section 1.6 to 1.7 summarises the HRs used in the model to estimate PFS and OS. Table A below summarises the modelled PFS and OS gains.

Figure 3. Entrectinib and PEM+PLAT PFS curves: PEMT+PLAT estimated using HR from ASCEND-4 MAIC applied to entrectinib curve (ERG's approach).

Source: ERG figure 19

PFS (figure 3):

- **The company** (B.3.3.) in its preferred approach first estimated crizotinib curve using HR from MAIC using entrectinib (n=78) and crizotinib data (n=53) from PROFILE 1001 (HR= [redacted], 95% CI: [redacted]; for more details see section B.2.9 in the company submission and clarification question A6). The HR was inverted and applied to the entrectinib curve to estimate crizotinib. Next the company used HR (0.45, 95% CI 0.35, 0.60) from PROFILE

1014 comparing crizotinib with PEM+PLAT (without maintenance therapy). The inverse of this HR was applied to crizotinib curve to estimate PEM+PLAT.

- The ERG was concerned with the apparent disconnect between the lack of a PFS benefit with entrectinib and the survival gains in the company's MAIC comparing entrectinib and crizotinib (table A). The PROFILE 1014 HR for OS was adjusted for cross-over as there was a high cross-over to crizotinib (84%). Further, the ERG notes that PROFILE 1014 PFS HR used by the company to estimate PEM+PLAT curve from the crizotinib curve were not accepted by the TA529 committee (ERG report section 4.4).
- The ERG preferred the company's alternative approach using HR from MAIC using entrectinib (n=78) and PEM+PLAT data (n=187) from ASCEND-4 (HR [redacted] 95% CI: [redacted]; see issue 3 for more details). The HR was inverted and directly applied to the entrectinib curve to estimate PEM+PLAT.

Figure 4. Entrectinib, crizotinib and PEM+PLAT OS curves: company's approach (PROFILE 1014) and ERG's approach (ASCEND-4)

Source: ERG figure 24

OS (figure 4):

- As with PFS, the company (B.3.3.) first estimated the crizotinib curve using the HR from MAIC using entrectinib (n=78) and crizotinib data (n=53) from PROFILE 1001 (HR= [redacted], 95% CI: [redacted]; for more details see section B.2.9 in the company submission and clarification question A6). The HR was inverted and applied to the entrectinib curve. Next, the HR (adjusted for crossover; 0.346, 95% CI 0.081, 0.718) from PROFILE 1014 comparing crizotinib with PEM+PLAT (without maintenance therapy) was inverted and applied to the crizotinib curve to estimate PEM+PLAT. There was a high cross-over to crizotinib (84%) and the unadjusted HR is 0.760 (95% CI: 0.548 to 1.053).
- Similarly, to PFS, the ERG was concerned with using the crizotinib MAIC. Instead, they used HR from the MAIC using entrectinib (n=78) and PEM+PLAT data (n=187) from ASCEND-4 (HR[redacted]95% CI: [redacted]). The HR was inverted and directly applied to the entrectinib curve to estimate PEM+PLAT.

Tables A and B compare the ERG's and company' approaches.

Table A. Modelled PFS, PPS and OS (undiscounted) using STARTRK-2 subgroup (n=78)

Time, months	Entrectinib	ERG's preferred approach		company's preferred approach	
		PEM+PLAT	Entrectinib gain	PEM+PLAT	Entrectinib gain
Mean OS	[redacted]	39.21	[redacted]	15.57	[redacted]
Median OS	[redacted]	26.6	[redacted]	10.8	[redacted]
Mean PFS	[redacted]	11.43	[redacted]	11.69	[redacted]
Median PFS	[redacted]	7.9	[redacted]	7.9	[redacted]
Mean PPS	[redacted]	27.78	[redacted]	3.87	[redacted]
Median PPS	[redacted]	18.7	[redacted]	2.9	[redacted]

Source: ERG model

Table B. Modelled percentage of patients alive using STARTRK-2 subgroup

Years	Entrectinib	PEM+PLAT ERG's preferred approach	PEM+PLAT company's preferred approach
2.0	[redacted]	54.1%	19.9%
4.0	[redacted]	28.1%	3.6%
5.0	[redacted]	20.5%	1.6%
10.0	[redacted]	4.2%	0.0%
15.0	[redacted]	0.8%	0.0%
30.0	[redacted]	0.0%	0.0%

Source: ERG model

The ERG's preferred approach suggests much shorter mean OS gain with PEM+PLAT than the company's approach ([redacted] respectively), the mean PFS gain is similar ([redacted] respectively), with the mean PPS gain being much longer with the company's preferred approach ([redacted] respectively). Notably, using the ERG's approach 20.5% of patients are estimated to be alive at 5 years while only 1.6% are estimated alive using the company's approach.

For a comparison, in TA529:

- The ERG noted: PPS gain with crizotinib of 19.2 months, and PFS gain of 9.6 months versus PEM+PLAT was not considered to be supported by evidence. PPS gain that is substantially larger than PFS gain (which translates into a greater OS treatment effect than PFS treatment effect) was questioned.
- The committee in TA529 concluded that the maximum expected survival benefit of crizotinib vs PEM+PLAT would be between 13.1 and 16.2 months.

Why this issue is important

To be able to assess the clinical- and cost-effectiveness of entrectinib, it is important to identify the most appropriate way of estimating PFS and OS for PEM+PLAT.

Technical team preliminary judgement and rationale	The technical team considers the ERG' approach estimating PEM+PLAT using HRs from ASCEND-4 MAIC more suitable than the company's because: • it does not require estimating crizotinib first, • of the uncertainty around OS HR from PROFILE 1014 due to high level of cross-over, and because ASCEND-4 trial used maintenance therapy, • the entrectinib survival gains are clinically plausible. It considers the modelled survival gain with entrectinib vs PEM+PLAT of [redacted] months to be clinically plausible, however it notes that the modelled survival with PEM+PLAT of 39.21 months is surprisingly high (see issue 5). The technical team considers the results suitable for decision making. However, it notes that the results are extrapolated from PFS and OS values with high level of uncertainty (see issue 3) and that the choice of OS/PFS modelling has a large effect on the cost-effectiveness results.

Issue 5 – End-of-Life

Questions for engagement	5a. What is the mean survival of people with advanced ROS1-positive NSCLC who are treated with PEM+PLAT induction followed with pemetrexed maintenance treatment? 5b. Is it plausible that entrectinib will increase the survival of people with advanced ROS1-positive NSCLC compared with PEM+PLAT induction followed with pemetrexed maintenance treatment by at least 3 months?
Background/description of issue	The NICE methods guide (6.2.10) states that the following criteria have to be met for a treatment to be considered life-extending treatment at the end of life: • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

The company provided evidence to support the consideration of entrectinib as an end of life treatment for locally advanced or metastatic ROS1-positive NSCLC). The company's evidence is summarised in table C below:

Table C End of life considerations

NICE criterion	Data highlighted by the company
Life expectancy, normally less than 24 months	Median OS in patients with ROS1-positive NSCLC not treated with ROS1-targeted treatment in Korean clinical practice was 20.0 months (Park et al. 2018).
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed-based chemotherapy in clinical trials ranges from 19.2 to 27.7 months across treatment settings (first- to third-line plus) but it should be noted that some patients went onto receive ROS1-targeted treatment post progression (ASCEND-4; Solomon et al. 18; PROFILE 1029; PROFILE 1007; ASCEND-5)
	Median OS in patients with ALK-positive NSCLC treated with pemetrexed plus platinum with pemetrexed maintenance in the first-line setting was 26.2 months in ASCEND-4 but this was not adjusted for crossover (43% of patients switched to ROS1-targeted treatment post progression).
	Median OS in patients with ALK-positive NSCLC who did not receive crizotinib in PROFILE 1001 was 20.0 months.
Sufficient evidence to indicate an extension to life, of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in the entrectinib integrated analysis, with only [redacted]% of patients having died at the time of the latest analysis (30 Oct 2018) when the minimum follow-up was [redacted] months (median follow-up [redacted] months).
	Median OS associated with crizotinib was 51.4 months in PROFILE 1001. KM plots of OS in MAIC estimate a survival advantage in favour of entrectinib versus crizotinib.
	Estimated LYG with entrectinib versus pemetrexed plus platinum with pemetrexed maintenance in the economic modelling is 4.49 years (base case).

Key: KM, Kaplan Meier; LYG, life years gained; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.
Source: Table 34 CS.

	The OS data for STARTRK-2 are immature (median OS was [redacted]) and the median PFS with entrectinib was [redacted]. **The technical team** notes that crizotinib is not considered to be a comparator in this appraisal (see issue 1 for more details). However, given the ERG's assumption of similar efficacy for entrectinib and crizotinib, crizotinib OS and PFS results from ROS1-positive NSCLC are summarised here: • PROFILE 1001 (n=53; 7 untreated and 46 had at least 1 prior chemotherapy), a single arm open-label study in advanced ROS1-positive NSCLC: o median OS was 51.4 months (4.28 years; 95% CI, 29.3–not reached) o median PFS was 19.3 months (1.6 years; 95% CI, 15.2–39.1). o A total of 26 deaths (49%) occurred (median follow-up period of 62.6 months), and of the remaining 27 patients (51%), 14 were in follow-up at data cut-off. The committee in TA529 agreed that crizotinib meets both criteria to be considered a life-extending treatment at the end of life (note that OS PROFILE 1001 data were not available at the time of the appraisal): *…. In the proxy population with ALK-positive NSCLC, median overall survival ranged from 6 months to 22 months and there is no evidence that it would be better in people with ROS1-positive advanced NSCLC. ... The committee agreed that crizotinib for ROS1-positive advanced NSCLC met the first criterion to be considered a life-extending treatment at the end of life. The committee noted that the mean overall survival gained with crizotinib, as estimated in the company's revised base case, was 18.2 months for untreated disease and 20.9 months for previously treated disease. Therefore, crizotinib may offer, on average, at least 3 months' extension to life compared with standard care. However, it … considered that any estimate of an overall survival gain compared with standard care was very uncertain. … The committee concluded that crizotinib met both criteria to be considered a life-extending, end-of-life treatment* (FAD section 3.15). Table A (issue 4) summarises the model's PFS, post-progression survival (PPS) and OS predictions. The company's approach suggests median OS of 15.57 months while the ERG's approach estimated 39.21 months.

	The ERG notes that the evidence presented by the company regarding life expectancy of less than 24 months to be inconsistent with results in the ERG's model.
Why this issue is important	To be able to assess the cost-effectiveness of entrectinib, it is important to establish if entrectinib is a life-extending treatment at the end of life compared with a pemetrexed treatment.
Technical team preliminary judgement and rationale	The technical team considered the following: • Survival on PEM+PLAT: o A retrospective Korean study of 103 patients with ROS1-positive NSCLC treated between January 2001 and February 2018 showed that the 45 patients who did not received tyrosine kinase inhibitors achieved median OS of 20.7 months (95%CI 8.4 to 54.3). o TA529 considered that PEM+PLAT survival is < 24 months. o The model suggests mean OS of 39.21 months and median OS of 26.6 months for PEM+PLAT (issue 4). • Survival gain with entrectinib: o The entrectinib survival data are immature (median PFS of 14.8 months was reported in STARTRK-2 subgroup). o PROFILE 1001 suggests median OS of 51.4 months for crizotinib. o TA529 considered that survival gain with crizotinib versus PEM+PLAT is ≥ 3 months. o The model suggests entrectinib mean survival gain of [redacted] months and median survival gain of [redacted] months versus PEM+PLAT (issue 4). It has been accepted that the life expectancy of patients treated with PEM+PLAT is less than 24 months in a recent appraisal in ROS1-positive NSCLC (TA529). Although the model in this case predicts that survival with PEM+PLAT is longer than 24 months, the technical team considers, that based on precedence, entrectinib is likely to meet both criteria to be considered a life-extending, end-of-life treatment when compared with pemetrexed treatment. However, it notes that the clinical evidence does not seem to be consistent with the model outputs for PEM+PLAT.

Issue 6 – Pemetrexed maintenance therapy

Questions for engagement	6. What is the average duration of maintenance therapy with pemetrexed? • Is assuming 8 cycles of maintenance therapy after 4 cycles of induction as used in the ERG scenario based on ASCEND-4 trial appropriate?
Background/description of issue	For the comparator PEM+PLAT, **the company** assumed: • No maintenance therapy in the base case (note PEM+PLAT is estimated from PROFILE 1014 that did not use maintenance therapy) and PEM+PLAT induction is assumed to be given for 6 cycles in line with the SmPC and TA529 • In a scenario of estimating PEM+PLAT using MAIC from ASCEND-4, 4 cycles of PEM+PLAT induction are followed with 4 cycles of maintenance therapy post-progression to align this assumption with the clinical evidence. • In the scenario, pemetrexed maintenance therapy can be given only after pemetrexed with cisplatin as per TA402 and therefore it is excluding patients who received pemetrexed with carboplatin. Current clinical practice has changed recently. The CDF list's Blueteq specifies that pemetrexed is given as maintenance therapy following induction chemotherapy with pemetrexed in combination with either carboplatin or cisplatin and which has not progressed immediately after 4 cycles of such chemotherapy. The ERG's clinical experts suggested that maintenance therapy is generally given until progression of disease, for a maximum of 2 years or 20 cycles of treatment. The ERG considers the company's approach (no maintenance treatment in the base case and 4 cycles when using ASCEND-4 MAIC) may underestimate the mean number of treatment cycles expected to be received for maintenance. The ERG therefore assumed: • pemetrexed maintenance therapy after both cisplatin and carboplatin; and • maintenance costs until progression and for a maximum of 2 years (mean time to progression is 11.43 months with median of approximately 12 cycles) in its preferred base case as this is a more accurate reflection of UK clinical practice (although this is not based

	on the clinical trial evidence). Induction is assumed to be used for 4 cycles in line with the ASCEND-4 data. • In addition, they explored a scenario analysis aligning the use of maintenance therapy with ASCEND-4 data and assumed 8 maintenance cycles; and • a scenario analysis assuming 6 cycles for maintenance therapy based on clinical experts' advice of a clinically plausible median duration. • In both scenario analyses induction is assumed to be given for 4 cycles.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of entrectinib, it is important to understand current clinical practice around pemetrexed maintenance therapy.
Technical team preliminary judgement and rationale	**The technical team** agrees with the ERG. To reflect current clinical practice and to align the clinical evidence with ASCEND-4, it assumed that pemetrexed maintenance therapy is given for 8 cycles after induction with pemetrexed in combination with either cisplatin or carboplatin. It notes that assumptions around maintenance duration have large effects on the results. This assumption was incorporated into table 1.

Issue 7 – Subsequent treatments

<table>
<tr><td>Questions for engagement</td><td>7a. Do you consider that all people with advanced ROS1-positive NSCLC who have discontinued first line-treatment would be given subsequent treatments?
7b. Do you consider that PEM+PLAT would be the second-line treatment after entrectinib?
7c. Do you consider that atezolizumab (TA584) should be included in the cost of subsequent treatments?</td></tr>
<tr><td>Background/description of issue</td><td>The company (section B.3.5.) used data from the entrectinib clinical trials (STARTRK-1 and STARTRK -2) to estimate the proportion of patients expected to receive certain subsequent treatments after progression. These proportions were adjusted for clinical expert opinion and are summarised in table D.
The average one-off cost of subsequent therapy was £4,815 and £3,541 for the entrectinib and pemetrexed plus platinum arm respectively (note the costs do not include the pemetrexed maintenance discount because it is confidential), which was applied upon progression.

Table D. Proportions of subsequent treatments assumed in the model by the company
<table><tr><th>Subsequent therapy</th><th>Entrectinib</th><th>PEM+PLAT</th></tr><tr><td>Pemetrexed</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Carboplatin</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Cisplatin</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Nivolumab</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Crizotinib</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Docetaxel</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Gemcitabine</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Paclitaxel</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Pemetrexed disodium</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Bevacizumab</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Erlotinib</td><td>[redacted]</td><td>[redacted]</td></tr></table></td></tr>
</table>

	Source: Modified table 37 ERG report The ERG noted that, one-off cost of subsequent therapy should include all lines of subsequent treatment and not just the second line. The ERG was concerned with the proportions of subsequent treatments applied by the company in the economic model. These data are based on entrectinib trials and may not reflect treatments used in all trials used to inform the treatment effectiveness. Subsequent treatments received in PROFILE 1001 were not reported by the company, and therefore, this remains an outstanding source of uncertainty in the model. There is a potential disconnect between the effects and costs applied, which could bias the cost-effectiveness results. Further to this, these treatments do not fully reflect UK clinical practice, as most patients would be expected to receive PEM+PLAT after entrectinib. • During clarification, the ERG has requested a scenario testing the impact of applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib. The ERG assumed PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib (the company's clarification scenario analysis) in its preferred base case. The ERG is also concerned that the number of subsequent treatments received in the company's base case model is based on just [redacted] of the total number of patients. • The ERG's clinical experts advised that approximately 100% of patients would be expected to receive subsequent treatments after progression. • The total number of patients receiving subsequent treatments the STARTRK-2 subgroup was [redacted]. The ERG is unclear why the proportion of patients receiving subsequent treatments is so low in the trials (when approximately 70% of patients had progressed in the ERG's preferred efficacy set). The ERG assumed that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments (however this approach needs to be caveated by the fact that it is not based on the underlying trial data for entrectinib). The average one-off cost of subsequent therapy in the ERG's preferred base case is £8,478 and £14,336 for the entrectinib and pemetrexed plus platinum arms respectively (note the costs do not include the pemetrexed maintenance discount because it is confidential).

Why this issue is important	To be able to calculate the cost of subsequent treatments, it is important to understand current clinical practice around subsequent treatments.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG approach and to reflect UK clinical practice incorporated the ERG's changes into table 1: • assumed PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib. • assumed that 100% of patients who have discontinued first line treatment are expected to receive subsequent treatments However, this approach is not based on the underlying clinical data and includes only second-line subsequent treatments costs. Further, that this approach does not include treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel which was recommended in June 2019 as an option for some people with metastatic NSCLC (TA584).

Issue 8 – Utilities

Questions for engagement	8. Do you consider the ERG's or the company's utility values more appropriate? • ERG: utility values accepted in TA529 (PFS=0.81 and PPS=0.66) • Company: PFS utility estimated from STARTRK-2 (0.73) and PPS utility value from TA529 (0.66).
Background/description of issue	**The company** (section B.3.4.1.) applied a linear mixed model to EQ-5D-3L data from STARTRK-2. The model included sex, extent of the metastasis, age, and time from treatment started due to limited observations. Following a step-wise selection all fixed effects were removed. To capture the correlations between repeated assessments per patient, a random effect for intercept and slope were included as random effects in the statistical model. • The final model results in a mean PFS utility of 0.73 (95% CI: 0.64, 0.83). • For the PPS health state, the company used utility of 0.66 from TA529 in ALK-positive NSCLC, as there were insufficient data to provide a reliable estimate. • The same utilities were assumed for comparators consider in the submission. • During clarification, the company run a number of scenario analyses including a scenario using utilities accepted in TA529 (PFS=0.81; PPS=0.66). The ERG commented, that the company did not provide much detail about its analysis of the EQ-5D data. • From a methodological point of view the company's approach is reasonable, however, the ERG was concerned that the company did not implement the results of the regression model correctly and considers the company's estimate for the PFS health state to be flawed. • Secondly, by using different data sources to inform different health states, the correlation between health state is lost with this approach. The relationship between the values of each

	health state are likely to be a more influential driver in the economic model than the baseline utility scores. • The ERG ran a scenario analysis using the company's raw mean utility values from STARTRK-2 of [redacted] for PFS and [redacted] for PPS, but considers the use of data previously accepted by the committee at TA529 to be a more robust approach. The ERG therefore uses values accepted in TA529 (PFS=0.81; PPS=0.66) in its preferred base case.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of entrectinib, it is important to identify the most appropriate utilities for PFS and PPS states.
Technical team preliminary judgement and rationale	The technical team prefers trial-based utility data, but also that there is consistency across all data sources used in the model. Given that only one set of utility data comes from the trial and that the regression model hasn't been implemented correctly, the ERG approach is preferred. The utility values accepted in TA529 (PFS=0.81; PPS=0.66) are incorporated in table 1.

Issue 9 – Health care cost

<table>
<tr><td>Questions for engagement</td><td>9. From looking at table E, is the ERG's or the company's approach to resource use for the PFS and PPS health states more appropriate?</td></tr>
<tr><td>Background/description of issue</td><td>The company's (section B.3.5.) approach is summarised in table E. Different resource requirements in the PFS state compared to the PPS health state were used. Monitoring costs assumptions were sourced from TA529. These estimates have also been used in other technology appraisals in NSCLC including TA406 and TA296 (replaced by TA422) and TA258. In line with TA529, it is assumed that all treatment arms would require the same resource use.
Table E. Comparison of company's and ERG's preferred disease management resource use
<table>
<tr><th rowspan="3">Resource required</th><th colspan="4">Company's assumptions</th><th colspan="4">ERG's clinical expert assumptions</th></tr>
<tr><th colspan="2">PFS</th><th colspan="2">PPS</th><th colspan="2">PFS</th><th colspan="2">PPS</th></tr>
<tr><th>% patients</th><th>Frequency per month</th><th>% patients</th><th>Frequency per month</th><th>% patients</th><th>Frequency per month</th><th>% patients</th><th>Frequency per month</th></tr>
<tr><td>Outpatient visit</td><td>100%</td><td>0.75</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td></tr>
<tr><td>GP visit</td><td>10%</td><td>1.00</td><td>28%</td><td>1.00</td><td>10%</td><td>0.33</td><td>28%</td><td>1.00</td></tr>
<tr><td>Cancer nurse</td><td>20%</td><td>1.00</td><td>10%</td><td>1.00</td><td>20%</td><td>0.33</td><td>50%</td><td>1.00</td></tr>
<tr><td>Complete blood count</td><td>100%</td><td>0.75</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td></tr>
<tr><td>Biochemistry</td><td>100%</td><td>0.75</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td><td>100%</td><td>1.00</td></tr>
<tr><td>CT scan</td><td>30%</td><td>0.75</td><td>5%</td><td>0.75</td><td>100%</td><td>0.50</td><td>30%</td><td>0.75</td></tr>
<tr><td>Chest X-ray</td><td>30%</td><td>0.75</td><td>30%</td><td>0.75</td><td>0%</td><td>0.00</td><td>0%</td><td>0.00</td></tr>
</table></td></tr>
</table>

	Source: ERG report Table 39 Key: differences highlighted in bold. The ERG's clinical experts considered some of the company's assumption not to be reflective of UK clinical practice. Therefore, the ERG tested the impact of the expert's corrected resource use for PFS and PPS health states in a scenario analysis. A comparison of the company's base case inputs with the ERG's clinical expert informed inputs is given in table E. The ERG incorporated the clinical expert assumptions into its preferred base case.
Why this issue is important	To be able to calculate the health states cost, it is important to understand current clinical practice around disease management.
Technical team preliminary judgement and rationale	The technical team considers it appropriate to apply the ERG's preferred approach in order to reflect UK clinical practice. The technical team applied the ERG's preferred approach to table 1.

Issue 10 – Cancer Drugs Fund

Questions for engagement	10a. Does entrectinib meet the criteria for inclusion in the Cancer Drugs Fund? • Does entrectinib has plausible potential to be cost-effective? • Could data collection reduce the outstanding uncertainty identified in this report? 10b. What data would be most useful to collect to address the outstanding uncertainties?
Background/description of issue	**The company** have proactively positioned entrectinib for funding via the Cancer Drugs Fund (CDF) as opposed to by routine commissioning in the NHS. They also explained that a [redacted]. The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but would require information on its effectiveness before it can be considered for routine commissioning (when the guidance is reviewed). The arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016 are specified in NICE's Cancer Drugs Fund methods guide (addendum).
Why this issue is important	If entrectinib is not recommended for routine commissioning, the committee will consider if it could be recommended for use within CDF.
Technical team preliminary judgement and rationale	The technical team considers that entrectinib meets the criteria for inclusion in the Cancer Drugs Fund: • It considers that entrectinib has plausible potential to be cost-effective, taking into account end-of-life criteria. • It considers that there is clinical uncertainty that could be reduced through data collection via ongoing studies. It notes, that the committee will be interested in the practicalities of data collection within the Cancer Drugs Fund, to ascertain the uncertainties identified in this report.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 1: Entrectinib compared with pemetrexed and platinum: technical team preferred assumptions and impact on the cost-effectiveness estimate. The technical team notes that considering the level of uncertainly around the ICER calculation, the most plausible ICER for entrectinib can be higher or lower than £28,824 per QALY gained. The ICERs include proposed PAS for entrectinib, but not the confidential discount for pemetrexed maintenance therapy. ICERs with all confidential discounts will be discussed by the committee.

Alteration		**Issue**	**ICER**	**Difference**
Company's base case using company's analysis set		**–**	**£15,628**	**-**
Company's base case using company's analysis set corrected for errors		**Table 3**	**£16,139**	**-**
Company's base case using STARTRK-2 subgroup analysis set		**Issue 2**	**£21,845**	
Company's base case assumptions:	**Technical team assumptions:**			
Including cost of ROS1 testing	**1.** Removing cost of ROS1 testing	Table 3	£19,566	-£2,279
PROFILE 1014 HR to estimate PEM+PLAT from crizotinib (PROFILE 1001 MAIC) and assuming 6 cycles of PEM+PLAT induction.	**2.** ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT. Plus changing the duration of PEM+PLAT induction to 4 cycles to match the duration in ASCEND-4	Issue 4	£52,399	+£30,554
Assumed no maintenance treatment with pemetrexed for PEM+PLAT	**3.** Assuming maintenance treatment after cisplatin and carboplatin for a median of 8 cycles in line with ASCEND-4	Issue 6	£18,351	-£3,494
Only a proportion of patients ([redacted] in STARTRK-2 subgroup) had subsequent treatments (while ~70% progressed)	**4.** Assuming that 100% of patients who discontinued first-line treatment receive subsequent treatments	Issue 7	£21,796	-£49
Range of subsequent treatments	**5**. PEM+PLAT for all patients who progress on entrectinib	Issue 7	£22,530	+£685
PFS utility of 0.73 from STARTRK-2 and TA529 value of 0.66 for PPS	**6.** Using TA529-accepted utility values of 0.81 for PFS and 0.66 for PPS	Issue 8	£21,232	-£613
Used estimates from other technology appraisals in NSCLC	**7.** Using the ERG's clinical expert's suggested resource for PFS and PPS states	Issue 9	£22,812	+£967
Cumulative impact of technical team assumptions (1 to 7)		**–**	**£28,824**	**+£6,979**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers: clinical evidence based on a small subgroup form STARTRK-2 trial	STARTRK-2, the key clinical trial is an ongoing single arm phase II basket trial in people with solid tumours that have a NTRK1/2/3, ROS1, or ALK gene fusion. It has so far recruited 207 patients. The ROS1-positive advanced NSCLC subgroup includes only 78 people (see issue 2 for more information).	Unknown.
Immature evidence base	The OS data for STARTRK-2 are immature (median OS [redacted]) and the median PFS with entrectinib was [redacted] The clinical evidence from the STARTRK-2 subgroup is based on a May 2018 enrolment data cut-off (database lock of 30 October 2018). The company highlighted that [redacted].	Unknown.
STARTRK-2: prior treatments	In the STARTRK-2 subgroup, 57 patients (73.1%) received one or more systemic treatments before entrectinib, leaving only 21 treatment-naïve patients (i.e. not having received prior systemic therapies). However, due to the small of the clinical evidence, it was not possible to differentiate between naïve and previously treated patients and so an "all-lines" approach has been used to maximise the patient numbers and robustness of the available data (see issue 2 for more information).	The available evidence is a more accurate representation of patients treated with entrectinib in second line rather than first line.
No comparative evidence available	Matching adjusted indirect comparison (MAIC) was conducted using data from PEM+PLAT data from the ASCEND-4 trial in ALK-positive NSCLC and using STARTRK-2 trial subgroup in ROS1-positive NSCLC (see	Unknown

	issue 3 for more details). The clinical -effectiveness estimates are therefore highly uncertain.	
Adverse events	The company's MAIC of discontinuation due to AEs suggest that a [redacted] proportion of patients taking entrectinib and PEM+PLAT discontinue treatment due to AEs ([redacted] vs 8.56%). The proportions of patients after reweighting are similar and the confidence interval around the OR is wide ([redacted]). But comparative data for specific AEs used in the economic model are based on unadjusted single-arm data for the company's preferred efficacy set (n = 53) and the PEM+PLAT arm of PROFILE 1014 (n = 171).	Unknown.
Time on treatment duration PEM+PLAT	No data for PEM+PLAT treatment duration is available. The company assumed 6 cycles of PEM+PLAT in its base case. ERG's clinical expert noted that 4 cycles of treatment is more common than 6 cycles of PEM+PLAT. However, when PEM+PLAT is estimated using ASCEND-4 MAIC (see Issue 4 for more details) the duration of treatment in the model is 4 cycles in the model, to match the duration of treatment with PEM+PLAT in ASCEND-4.	Unknown. For pemetrexed maintenance therapy, see issue 6.

Table 3: Other issues for information

Issue	Comments
ROS1 testing	ROS1 testing was included in the 2019/2020 National Genomic Test Directory and is a standard part of diagnostic work-up in NSCLC. ROS1 testing is considered to be routine practice for NSCLC and therefore the costs of ROS1-testing were removed from the company's and ERG's base case. The cost-effectiveness results reported in Table 1 are reflective of this change.
Errors in model	The ERG corrected, the half cycle correction application, the discounting of subsequent treatments, PSA calculations, the calculation of ROS1 costs, and the application of Health

	Resource Group costs for maintenance of AEs. All corrections had a small effect on the company's ICER (see table 1). The cost-effectiveness results reported in Table 1 are reflective of all ERG's corrections.
PFS	PFS in the STARTRK-2 was assessed by investigators and blinded independent central review (BICR), however the company submission only reports BICR. Sensitivity analysis using investigator PFS data was done for crizotinib MAIC as the company was unsure if BICR or investigator PFS was used in the crizotinib trial. The investigator PFS MAIC results were [redacted] However, the ERG considers the BICR measurement more robust. The cost-effectiveness results reported in Table 1 are based on BICR PFS extrapolation.
Company's review of cost-effectiveness evidence	The ERG considers that the company could have performed a broader SLR to incorporate a wider population. However, it noted, that it is unlikely that alternative sources with more robust and reliable data exists.
Incorrect values	Some of the reported treatment-related AEs used in the model no not match the values reported in the trial are they are taken from. The ERG tested the impact of the correct values for hypophosphatemia and elevated transaminases and found that it had a negligible impact on the ICER. The ERG considers it likely that the other reported AEs that were not captured in the company's model would also have a negligible impact and, therefore, the ERG does not have concerns regarding the company's exclusion of these.
Pulmonary embolism rates	The company assumed that 6.5% of PEM+PLAT patients experienced pulmonary embolism, while entrectinib (and crizotinib) patients were assumed to have 0%. However, it was reported that 6.4% of crizotinib patients experienced a pulmonary embolism in PROFILE 1014 data. The ERG removed the pulmonary embolism rates from the model in a scenario analysis with a minimal effect on the resulting ICERs.
Disutilities	Disutilities associated with AEs were sourced from a study that used a different elicitation technique to the NICE-preferred method and applied it in healthy volunteers who relied on descriptions of symptoms from clinicians. It is unlikely that the company could have identified a better source of data. The ERG ran a scenario to remove the AE disutilities and found that the company's base case ICER increased by only £10.

Scenario analysis of entrectinib and crizotinib	The company compared entrectinib with crizotinib in a scenario analysis. The company conducted MAIC to comparing entrectinib with crizotinib using data for crizotinib from PROFILE 1001 trial in ROS1-positive NSCLC. Results of this MAIC (using the STARTRK-2 subgroup data) are reported in section 1.7. In addition, the company estimated PEM+PLAT using HR from PROFILE 1014 study comparing crizotinib with PEM+PLAT (study without maintenance pemetrexed therapy) and applying it to a crizotinib curve in the model. The approach to estimating PEM+PLAT in the model is discussed in issue 5. The ERG's critiqued this analysis and assumed that the drugs have a similar effect in delaying progression and extending life (PFS/OS HRs=1). This is in line with conclusions reached in TA422, where an FDA analysis of trial- and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib), suggested that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence. The ERG incorporated the assumption of equal clinical efficacy between entrectinib and crizotinib in its preferred analysis.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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List of abbreviations

CDF, Cancer Drugs Fund

CNS, central nervous system

EQ-5D-3L, European Quality of Life-5-dimension-3 levels questionnaire

ERG, evidence review group

HR, hazard ratio

ICERs, incremental cost-effectiveness ratio

KM, Kaplan Meier

MAIC, matching adjusted indirect comparison

NSCLC, non-small cell lung cancer

OS, overall survival

PEM+PLAT, pemetrexed in combination with a platinum drug

PFS, progression free survival

PPS, post progression survival

QALY, quality adjusted life years

Glossary

Indirect comparison: An analysis comparing interventions that have not been compared directly within a head-to-head randomised trial.

Quality-adjusted life year (QALY): An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs incorporate changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social, and other factors) of life. Used to measure benefits in cost–utility analysis.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings are used. Statistical methods for meta-analysis may or may not be appropriate for application to the quantitative results from the different studies.

Utility: A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **18 October 2019.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Sophie Guest**
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.	**None**

Questions for engagement

Issue 1: Comparators	
1. Is pemetrexed in combination with a platinum drug (PEM+PLAT) the key comparator in this appraisal? In line with NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not considered a comparator in the appraisal.	Roche agrees that pemetrexed in combination with a platinum drug (PEM+PLAT) is the key comparator in this NICE appraisal. On progression after first line therapy, patients should be offered PEM + PLAT as second-line therapy. Prior to crizotinib funding through the CDF, PEM+PLAT was considered the standard of care for ROS1-positive NSCLC patients. In accordance with the ROS1-positive NSCLC treatment pathway, patients currently receive crizotinib as first line treatment, and is considered standard of care by the clinical community. However, in line with NICE's position on CDF drugs as comparators in appraisals, crizotinib is not considered the key comparator in the base case analysis, but has been explored in scenario analyses.
Issue 2: Population	
2. Is the ERG's STARTRK-2 subgroup (n=78) or the company's analysis set (n=53) more appropriate for decision making?	The primary efficacy set was pre-specified in the protocol in agreement with regulators in which both the FDA and the EMA agreed with the methodology to pool safety and efficacy data from the clinical studies, and included criteria such as ≥12 months follow-up based on feedback provided by the FDA, to ensure an adequate assessment of durability of response in a relatively mature and stable dataset. Roche agrees that the ERG's STARTRK-2 subgroup analysis set is also appropriate for decision making. It is a larger dataset (N=78) from a single Phase II study compared to the primary efficacy set (N=53), and all patients received the recommended starting dose of entrectinib. Furthermore, STARTRK-2 is the only Phase II study of entrectinib and the only study designed to assess efficacy outcomes; it was also the only study to assess tumour scans prospectively which may mean results for ORR and PFS are less biased. Patients included in the ERG's preferred efficacy analyses with shorter follow-up contribute data for the efficacy outcomes reflected in the economic model (OS and PFS) up to the point at which they are censored, although OS is

	immature regardless of the efficacy set chosen. Although some differences in outcomes across cohorts were observed, the overall results were consistent with the findings from our original submission, and therefore Roche agree to proceed in using the ERG's STARTRK-2 analysis.
Issue 3: Indirect comparison entrectinib versus pemetrexed	
3a. Do you consider the use of evidence for the comparator PEM+PLAT from ALK-positive populations as a proxy for ROS1-positive NSCLC appropriate in the absence of ROS1-positive evidence?	In the absence of available data, Roche consider the use of ALK-positive patients an appropriate proxy for ROS1-positive NSCLC. There are very limited data for ROS1-positive NSCLC patients, and there is no data for pemetrexed plus platinum in ROS1-positive NSCLC, therefore we have used the next best alternative. As highlighted in the submission, we acknowledge the limitations of this approach, mainly, that ROS1 fusions define a unique molecular subset of oncogenic drivers, and there is no way to quantify or adjust for differences in treatment effects that are attributable to the underlying gene fusion. Furthermore, the validity of using data from ALK clinical trials is dependent on the ability to assume that the two biologically similar but distinct subtypes of NSCLC are comparable. ALK-positive and ROS1-positive NSCLC are similar in terms of patient demographics (e.g. younger age, non-smoker or light smoking) and clinical characteristics (e.g. adenocarcinoma histologic type), and clinical consultation endorsed the approach in consideration of the data limitations. Furthermore, a proxy assumption was used in the recent NICE appraisal for crizotinib for treating ROS1-positive advanced NSCLC (TA529) (1). Although the committee acknowledged that using data from a proxy population is far from ideal, after taking into account the relatively small patient population and the clinical experts' views, they agreed to explore the proxy data in its decision-making.

3b. Do you consider the result of the indirect comparison of entrectinib with PEM+PLAT to be clinically plausible (figures 1 & 2 and tables A & B in issue 4)?	Roche do not consider the OS results (figure 1) of the ASCEND-4 indirect comparison of entrectinib with PEM+PLAT to be clinically plausible, as it considerably over-estimates the overall survival benefits of PEM+PLAT. However, Roche considers the PFS results (figure 2) of the indirect comparison to be clinically plausible, as the MAIC suggested a statistically significant benefit of entrectinib versus PEM+PLAT (HR [redacted]), and a realistic mean PFS with PEM+PLAT (11.43 moths), which is in line with other NSCLC appraisals. Roche acknowledge that there are two possible approaches to estimate the OS and PFS of PEM+PLAT, both of which contain high levels of uncertainty, mainly due to using evidence from ALK+ NSCLC and due to differences in prior and subsequent treatments used in the ASCEND-4 and STARTRK-2 trials. The ASCEND-4 MAIC suggests no statistically significant benefit of entrectinib versus PEM+PLAT (HR [redacted]), and the undiscounted modelled OS with PEM+PLAT reported a mean OS of 39.2 months, which is not clinically plausible. Having reviewed other NSCLC technology appraisals such as TA406 and TA557, where PEM+PLAT was included as the main comparator, the maximum mean OS reported by an ERG for PEM+PLAT was 22.7 months (2). In addition, in the ROS1 crizotinib appraisal TA529, the reported PEM+PLAT mean OS was 17.6 months (1). These values are more in line with clinical expert opinion who confirmed that the OS gain of entrectinib vs PEM+PLAT followed by maintenance therapy would likely fall between 12-24 months. The over-estimation of PEM+PLAT OS from the ASCEND-4 analysis is due to the uncertainty introduced by the cross-over from the PEM+PLAT arm to ALK inhibitors (52% to any ALK inhibitor and 43% to Ceritinib). In addition, in UK clinical practice patients generally receive targeted treatments prior to PEM+PLAT. As a result, the potential OS for chemotherapy is being over-estimated in the ERGs model to over 39 months, which is clinically implausible.
Issue 4: OS and PFS modelling	

4. What approach to estimating PEM+PLAT overall survival (OS) and progression free survival (PFS) is appropriate for decision making (figure 4 & 5)? • ERG's preferred approach: hazard ratios (HRs) from an indirect comparison of entrectinib with PEM+PLAT using data from ASCEND-4 (with maintenance therapy) to estimate PEM+PLAT curve. • Company's preferred approach: HRs from an indirect comparison of entrectinib with crizotinib using data from PROFILE 1001, and applying HRs comparing crizotinib with PEM+PLAT (without maintenance therapy) from PROFILE 1014 to the estimated crizotinib curve to model PEM+PLAT.	As mentioned in our response to issue 3, Roche recognise the uncertainty associated with their base-case approach in estimating the OS and PFS of PEM + PLAT, and acknowledge that there are two possible approaches, yet neither of them are without issues. The ERG approach involves the HRs from the MAIC of entrectinib with PEM+PLAT using data from the ASCEND-4 trial. In the ASCEND-4 trial, ceritinib was compared to platinum-based chemotherapy (pemetrexed plus cisplatin or carboplatin) at first-line followed by pemetrexed maintenance in ALK-positive NSCLC patients. The inverse of the estimated HR from the MAIC was then applied to the modelled entrectinib OS curve estimating the OS for the chemotherapy arm. The ERG suggest their approach is more reflective of UK clinical practice as patients would be prescribed pemetrexed maintenance after chemotherapy treatment with PEM + PLAT. Although this is accurate, this comparison is associated with the key limitation that it requires the assumption that ROS1 versus ALK gene fusion status is not in itself either prognostic or a treatment effect modifier once imbalances in other patient characteristics have been accounted for. In addition, the ERG approach doesn't take into consideration the crossover effect. As reinforced in issue 3, it is widely acknowledged that the modelled mean OS of 39 months with PEM+PLAT is clinically implausible and hugely over-estimates the survival benefits of PEM+PLAT due to the high use of ALK inhibitors after progression on PEM+PLAT. Roche's base case approach to estimating the OS and PFS of PEM+PLAT included using the published HR from PROFILE 1014 (first-line trial of crizotinib versus pemetrexed) and applying it to the estimated crizotinib OS. The HR for crizotinib versus PEM+PLAT was taken from the latest reported data cut from PROFILE 1014 (HR = 0.346). The rank preserving structural failure time model (RFPSTM) was used to adjust for crossover. The inverse of this HR was then applied to the modelled crizotinib OS curve in the model to estimate the OS for pemetrexed plus platinum. As the HR is applied to the OS curve for crizotinib in ROS1-positive NSCLC, any difference in expected outcomes between ALK-positive and ROS1-positive NSCLC is already adjusted for. A limitation to this approach is the PEM+PLAT arm does not include pemetrexed maintenance therapy, which may be used in clinical practice. Even so, the curve estimated using the published HR applied on the estimated crizotinib arm was deemed to be more reflective of what is seen in clinical practice. As highlighted in our response to issue 3, there are no data available for PEM+PLAT in the ROS1 population. Therefore, in any indirect comparisons for entrectinib versus pemetrexed plus platinum therapy an assumption of

	general comparability across the ROS1 and ALK+ populations are needed. In applying the PROFILE 1014 outcomes to the crizotinib arm of the model this assumption is replaced with an assumption that the relative treatment effect of crizotinib and PEM+PLAT is equivalent across the ROS1 and ALK+ populations. Roche accept that there is a rationale for using the ASCEND-4 study in the ERGs model as it included maintenance therapy which is more reflective of UK practice, however this is primarily a cost factor that could also be applied to Roche's model. The uncertainty introduced by the cross-over to TKIs in the PEM+PLAT arm of the ASCEND 4 study far outweighs the impact of pemetrexed maintenance as it increases median OS for PEM+PLAT significantly to over 39 months whereas pemetrexed maintenance mean OS gain in the NSCLC NICE appraisal TA402 was 3.9 months (3). Although there is OS gain associated with pemetrexed maintenance, the addition of 4 months is not enough to justify the unrealistic PEM+PLAT OS estimation from the ASCEND-4 study. As such, whilst neither model is optimal, we believe firmly that Roche's base case model produces the most clinically plausible results and is therefore the most appropriate for decision making. It is important to note that with either approach, entrectinib was shown to be cost-effective.
Issue 5: End-of-Life	
5a. What is the mean survival of people with advanced ROS1-positive NSCLC who are treated with PEM+PLAT induction followed with pemetrexed maintenance treatment?	As demonstrated in both Roche's base case and the ERG's base case, entrectinib increases the survival of patients with advanced ROS1-positive NSCLC compared with PEM+PLAT induction followed with pemetrexed maintenance treatment by at least 3 months. The undiscounted entrectinib mean OS gain is [redacted] months [redacted] vs 15.6 months) in Roche's base case and [redacted] months ([redacted] vs 39.2 months) in the ERG's preferred approach. In both scenarios, the survival gain associated with entrectinib is greater than 3 months. Clinical expert opinion confirmed that although Roche's base case analysis under values the OS benefit of PEM + PLAT and the ERG approach over predicts the PEM+PLAT OS, the average OS associated with PEM + PLAT is generally below 24 months. Furthermore, crizotinib met the end-of-life criteria vs PEM+PLAT in two appraisals, TA529 and TA406, and the survival benefit of PEM+PLAT followed by maintenance therapy has not improved since the final decision of these submissions (1, 4).
5b. Is it plausible that entrectinib will increase the survival of people with advanced ROS1-positive NSCLC compared with PEM+PLAT induction followed with pemetrexed maintenance treatment by at least 3 months?	

Issue 6: Pemetrexed maintenance therapy	
6a. What is the average duration of maintenance therapy with pemetrexed? 6b. Is assuming 8 cycles of maintenance therapy after 4 cycles of induction as used in the ERG scenario based on ASCEND-4 trial appropriate?	Clinical expert opinion suggested that in clinical practice, it is unlikely for patients to receive 8 cycles of maintenance therapy after induction treatment. As requested by the NICE technical team, Roche have performed scenario analyses using 4 cycles and 6 cycles of maintenance therapy. The Roche base case applied a maximum of 4 cycles. As can be seen from Table 2 and Table 3, reducing the number of maintenance therapy cycles to 4 or 6 increases the ICER to £40,997 and £38,704, respectively. It is important to note that these scenarios are not particularly informative as they are cost-only scenarios that don't take into consideration any change in progression or survival benefit which may occur when reducing the number of maintenance therapy cycles. If the ASCEND-4 study is used as the base-case analysis, 8 cycles of maintenance therapy should be applied so the cost remains reflective of what was used in the study, otherwise the costs are being reduced without the survival benefits reducing in correlation.
Issue 7: Subsequent treatments	
7a. Do you consider that all people with advanced ROS1-positive NSCLC who have discontinued first line-treatment would be given subsequent treatments?	Roche's base case used STARTRK-2 trial data to determine the proportion of patients who received subsequent therapy. Therefore, the entrectinib OS outcomes are based on the [redacted] that received subsequent therapy in the trial. As discussed on the technical engagement call, clinical expert opinion suggested that it was unrealistic to assume 100% of patients who have discontinued first line treatment would receive subsequent treatments, and a realistic proportion that they would expect to see in clinical practice would be 60% or 70%. Therefore, as requested by the NICE technical team Roche have performed scenario analyses using 60% and 70%. Please note, in these scenarios the proportion who received subsequent therapy after receiving PEM+PLAT is set to equal the proportion who received subsequent treatment after entrectinib. As can be seen from Table 4 and Table 5, reducing the proportion who received subsequent therapy reduces the ICER to £35,161 and £35,538, respectively.

	Although reducing the proportion of patients who receive subsequent therapy reduces the ICER, it is important to note that this a cost-only scenario that doesn't take into consideration the OS benefit that would change in parallel with changing the proportion. As the OS for entrectinib is based on trial data, changing the proportion who received subsequent therapy only changes the costs without changing the survival benefits, and therefore the results are not overly informative for decision making.
7b. Do you consider that PEM+PLAT would be the second-line treatment after entrectinib?	Roche agrees with the ERG that applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib is more reflective of UK clinical practice than trial data.
7c. Do you consider that atezolizumab (TA584) should be included in the cost of subsequent treatments?	Clinical experts were in agreement that it is not necessary to consider atezolizumab in the cost of subsequent treatments. In clinical practice, if the patient has already received PEM+PLAT, clinicians would be hesitant to prescribe an immunotherapy such as atezolizumab in a ROS1-positive population and would use docetaxel instead. Therefore we do not consider that atezolizumab should be included in the cost of subsequent treatments.
Issue 8: Utilities	
8. Do you consider the ERG's or the company's utility values more appropriate? • ERG: utility values accepted in TA529 (PFS=0.81 and PPS=0.66) • Company: PFS utility estimated from STARTRK-2 (0.73) and PPS utility value from TA529 (0.66).	Roche agrees with the ERG that using one data source to inform health state utilities is preferable, and therefore considers the ERG's utility values more appropriate.
Issue 9: Health care cost	
9. From looking at table E, is the ERG's or the company's approach to resource use for the PFS and	Roche is in agreement that the ERG's approach to resource use for the PFS and PPS health states is more appropriate. Roche's assessment of resource use in the PFS and PPS health states were sourced from the crizotinib ROS1-positive NSCLC appraisal (TA529) (1). These estimates have also been used in other NSCLC

PPS health states more appropriate?	technology appraisals including TA406, TA296 (replaced by TA422) and TA258 (4-6), and were therefore viewed as the best available estimates as they have been subject to review by NICE ERGs and appraisal committees. However, we note that some of the assumptions may not be considered to be fully reflective of UK clinical practice, and therefore the alternative values proposed by the ERG's clinical experts are more appropriate and reflective of UK clinical practice.
Issue 10: Cancer Drugs Fund	
10a. Does entrectinib meet the criteria for inclusion in the Cancer Drugs Fund? • Does entrectinib has plausible potential to be cost-effective? • Could data collection reduce the outstanding uncertainty identified in this report?	Roche agrees with the NICE technical team's view that entrectinib meets the criteria for inclusion into the CDF. As discussed in our response to Issue 5, entrectinib comprehensively meets both end-of-life criteria. Entrectinib is cost-effective vs PEM+PLAT, evident by our preferred ICER of £21,845 and the technical teams most plausible ICER of £36,728, both of which fall under the maximum end-of life threshold. Roche has proactively proposed entry of entrectinib into the CDF as we acknowledge that there are a number of clinical- and cost-effectiveness uncertainties due to the limited and immature data. Longer-term, comparative data in a larger number of patients with ROS1-positive NSCLC would improve the robustness of the economic evaluation presented and reduce the outstanding uncertainty.
10b. What data would be most useful to collect to address the outstanding uncertainties?	Roche's proposed data collection concepts are summarised in Table 6, categorised by the areas of uncertainty highlighted in Table 2 of the technical report. Data collected by Public Health England (PHE) during a CDF period has the potential to help address a broad range of uncertainties; however, we acknowledge that the nature, scope and quality of data collected by PHE is yet to be determined and so we have not designated particular uncertainties to this method. Roche will collaborate closely with NICE, NHS England and PHE to help determine this, and to further elaborate on our currently existing proposals through the drafting of a data collection agreement. Roche are currently waiting to receive additional data from the integrated analysis; the day 180 data requested by the EMA. We have not yet received the data, however we know that there are an [redacted], in addition to the original 53. We aim to confirm timelines for receiving this data and updated analyses as soon as possible.

	In addition [redacted]. An overview of the CNS benefits of entrectinib vs crizotinib is provided in Appendix 1: Benefits of entrectinib vs crizotinib in targeting CNS metastases.

Table 1. NICE technical team base case results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+PLAT	37,264	2.91	2.05	[redacted]	[redacted]	[redacted]	£36,728
Entrectinib	[redacted]	[redacted]	[redacted]				

Table 2. Pemetrexed maintenance therapy: 4 cycles

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+PLAT	33,746	2.91	2.05	[redacted]	[redacted]	[redacted]	£40,997
Entrectinib	[redacted]	[redacted]	[redacted]				

Table 3. Pemetrexed maintenance therapy: 6 cycles

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+PLAT	35,636	2.91	2.05	[redacted]	[redacted]	[redacted]	£38,704
Entrectinib	[redacted]	[redacted]	[redacted]				

Table 4. Subsequent treatments: Trial proportion (60%)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+PLAT	34,809	2.91	2.05	[redacted]	[redacted]	[redacted]	£35,161
Entrectinib	[redacted]	[redacted]	[redacted]				

Table 5. Subsequent treatments: 70%

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+PLAT	35,399	2.91	2.05	[redacted]	[redacted]	[redacted]	£35,538
Entrectinib	[redacted]	[redacted]	[redacted]				

Table 6. Roche's CDF data collection proposals

Uncertainty/data gap	Data collection proposals
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix 1: Benefits of entrectinib vs crizotinib in targeting CNS metastases

NSCLC has a high propensity to metastasise to the central nervous system (CNS). Among patients with NSCLC, between 10% to 25% of patients present with CNS metastases at the time of diagnosis and up to 50% will develop CNS metastases at some point during the course of their disease (7-11). Due to the small ROS1-positive NSCLC patient population, limited data are available for the numbers of patients with CNS metastases at the time of diagnosis. Furthermore, results from available studies are variable as CNS metastases incidence is reported in 19%–53% of patients with ROS1-positive NSCLC (12-14).

CNS metastases (including brain metastases) in advanced NSCLC are a major clinical issue and are associated with a significant reduction in quality of life and estimated life expectancy. There is an unmet medical need for targeted treatment options that offer improved clinical effectiveness including extracranial and intracranial activity, and improved tolerability at earlier lines of treatment for patients with ROS1 NSCLC, to delay the use of increasingly ineffective non-targeted options at later lines. The need for a drug with good intracranial activity within this population was confirmed by external clinical expert opinion.

Crizotinib is currently the only targeted therapy licensed for use in advanced ROS1-positive NSCLC. However, crizotinib lacks proven CNS efficacy, which is important as approximately 19%–53% of patients with ROS1-positive NSCLC develop CNS metastases (12-14). Entrectinib is the first ROS1 Inhibitor to show intracranial activity against ROS1-driven CNS metastases, which has led to entrectinib receiving Promising Innovative Medicine (PIM) designation for the patient group (PIM 2018/0021).

Entrectinib demonstrated clinically meaningful and durable systemic responses in patients irrespective of the presence of CNS metastases at baseline. At the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), in patients with and without CNS metastases at baseline, ORR was [redacted] and [redacted] and DoR among responders was [redacted] months and [redacted], respectively. Systemic PFS observed in patients with and without CNS metastases at baseline was meaningfully durable ([redacted] months and [redacted] months, respectively), indicating activity against CNS metastatic disease and a possible protective effect against CNS progression. Furthermore, at the time of the primary integrated efficacy analyses (CCOD of 31 May 2018), in patients with CNS metastases at baseline and measurable disease, IC-ORR was [redacted] IC-DOR among responders was [redacted] months, and median IC-PFS was [redacted] months. Data at the time of the updated integrated efficacy analysis (CCOD of [redacted]), was similar to those observed in the primary integrated efficacy analysis

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Technical engagement response form

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **18 October 2019.**

Thank you for your time.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second, fully redacted, version of your comments (AIC/CIC shown as [redacted]). See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote

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About you

Your name	**Yvonne Summers**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**The Christie NHS Foundation Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Comparators	
1. Is pemetrexed in combination with a platinum drug (PEM+PLAT) the key comparator in this appraisal? In line with NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not considered a comparator in the appraisal.	**Yes, given that CDF drugs are excluded.**
Issue 2: Population	
2. Is the ERG's STARTRK-2 subgroup (n=78) or the company's analysis set (n=53) more appropriate for decision making?	**The ERG's model fits more with clinical practice in that the single RP2D is used.** **The company's model has longer follow up which is likely to be more helpful with modelling.**
Issue 3: Indirect comparison entrectinib versus pemetrexed	
3a. Do you consider the use of evidence for the comparator PEM+PLAT from ALK-positive populations as a proxy for ROS1-positive NSCLC appropriate in the absence of ROS1-positive evidence?	This is not ideal but reasonable as outcomes appear fairly similar from the limited data available.
3b. Do you consider the result of the indirect comparison of entrectinib with PEM+PLAT to be clinically plausible (figures 1 & 2 and tables A & B in issue 4)?	The estimates of survival for PEM + PLAT in the ERG's model are implausibly high. There is uncertainty around the entrectinib data, but it appears reasonable.

Issue 4: OS and PFS modelling	
4. What approach to estimating PEM+PLAT overall survival (OS) and progression free survival (PFS) is appropriate for decision making (figure 4 & 5)? • ERG's preferred approach: hazard ratios (HRs) from an indirect comparison of entrectinib with PEM+PLAT using data from ASCEND-4 (with maintenance therapy) to estimate PEM+PLAT curve. • Company's preferred approach: HRs from an indirect comparison of entrectinib with crizotinib using data from PROFILE 1001, and applying HRs comparing crizotinib with PEM+PLAT (without maintenance therapy) from PROFILE 1014 to the estimated crizotinib curve to model PEM+PLAT.	There are arguments for both. Some maintenance therapy is used in clinical practice, but even in maintenance trials the rates of getting onto maintenance treatment are around 50% Many patients still do not go onto maintenance therapy for a variety of reasons: - some have had enough after 3 months of chemo and want a treatment break - Some progress - Some have toxicity preventing further treatment - The evidence for maintenance pemetrexed is only after cisplatin and some clinicians will recommend sticking to the evidence base and therefore not use it after carboplatin - Furthermore if maintenance pem is used in less fit patients after carboplatin then the median number of cycles is fewer - likely only to be 3 or 4 - The survival modelling from the ERG's approach is implausibly high.
Issue 5: End-of-Life	

5a. What is the mean survival of people with advanced ROS1-positive NSCLC who are treated with PEM+PLAT induction followed with pemetrexed maintenance treatment?	This is difficult to estimate as, now that we are identifying this group of patients prospectively, they are benefitting from Crizotinib via the CDF and living longer. We do know, however, from audits of NSCLC patients with other molecular drivers (eg ALK) prior to widespread use of TKI's, that their median survival was < 24months and so it is reasonable to expect that this is also the case for patients with ROS1
5b. Is it plausible that entrectinib will increase the survival of people with advanced ROS1-positive NSCLC compared with PEM+PLAT induction followed with pemetrexed maintenance treatment by at least 3 months?	Yes, definitely so.
Issue 6: Pemetrexed maintenance therapy	
6a. What is the average duration of maintenance therapy with pemetrexed?	As discussed in 4,a conservative estimate is that 50% will not get maintenance at all, and of those who do get it the average number of cycles is likely to be 3-4.
6b. Is assuming 8 cycles of maintenance therapy after 4 cycles of induction as used in the ERG scenario based on ASCEND-4 trial appropriate?	No
Issue 7: Subsequent treatments	
7a. Do you consider that all people with advanced ROS1-positive NSCLC who have discontinued first line-treatment would be given subsequent treatments?	No, this in never the case. There are always patients who don't get a further treatment - historically in NSCLC the rate was only 25% of patients who went on to get a second treatment, but it is likely to be closer to 50% with modern treatments
7b. Do you consider that PEM+PLAT would be the second-line treatment after entrectinib?	Yes

7c. Do you consider that atezolizumab (TA584) should be included in the cost of subsequent treatments?	There is evidence that patients with molecular drivers do not derive significant benefit with single agent immunotherapy and of concern, there is a growing body of evidence that if immunotherapy is used prior to TKIs, then toxicity can be substantially enhanced. Single agent immunotherapy is the very last treatment option to be considered, and should be avoided if possible.
Issue 8: Utilities	
8. Do you consider the ERG's or the company's utility values more appropriate? • ERG: utility values accepted in TA529 (PFS=0.81 and PPS=0.66) • Company: PFS utility estimated from STARTRK-2 (0.73) and PPS utility value from TA529 (0.66).	The utility values are similar. The company has used trial QoL data which seems appropriate.
Issue 9 Health care cost	
9. From looking at table E, is the ERG's or the company's approach to resource use for the PFS and PPS health states more appropriate?	Both are inaccurate in different places. The Company underestimates scans, visits and blood tests and over estimates CXR in the PFS. It overestimates visits and blood tests in the PPS and underestimates scans. The ERG overestimates scans in the PFS and visits and blood tests in the PPS, but overall is closer to real life resource use.
Issue 10: Cancer Drugs Fund	

10a. Does entrectinib meet the criteria for inclusion in the Cancer Drugs Fund? • Does entrectinib has plausible potential to be cost-effective? • Could data collection reduce the outstanding uncertainty identified in this report?	Yes to all 3 questions. ROS-1 is a true molecular driver and longer follow up is likely to demonstrate substantially improved outcomes with Entrectinib
10b. What data would be most useful to collect to address the outstanding uncertainties?	Time on treatment, data on subsequent therapies, OS

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Technical engagement response form

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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)	**BTOG-NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Comparators	
1. Is pemetrexed in combination with a platinum drug (PEM+PLAT) the key comparator in this appraisal? In line with NICE's position statement on CDF drugs as comparators in subsequent appraisals, crizotinib is not considered a comparator in the appraisal.	Crizotinib would be the preferred comparator. However, given NICE's position statement on CDF drugs we agree that the most appropriate comparator should, therefore, be platinum and pemetrexed.
Issue 2: Population	
2. Is the ERG's STARTRK-2 subgroup (n=78) or the company's analysis set (n=53) more appropriate for decision making?	We agree that the ERG's STARTRK-2 subgroup (n=78) is the preferable dataset to use for analysis given the inclusion of larger patient numbers and focus on patients treated at the RP2D. The only factor for consideration is that ORR may not be fully reflected by inclusion of patients with shorter follow-up as response may not yet have been achieved. However, this is likely to have minimal impact given PFS and OS are more relevant for decision-making.
Issue 3: Indirect comparison entrectinib versus pemetrexed	
3a. Do you consider the use of evidence for the comparator PEM+PLAT from ALK-positive populations as a proxy for ROS1-positive NSCLC appropriate in the absence of ROS1-positive evidence?	On balance, in the absence of data from a ROS1-positive NSCLC randomised trial, it is reasonable to use data from an ALK-positive population. However, it is uncertain how similar the two populations (ALK and ROS1 NSCLC) are in terms of prognosis and outcomes with chemotherapy.
3b. Do you consider the result of the indirect comparison of entrectinib with PEM+PLAT to be	The progression-free survival figures appear plausible across the datasets. However, it seems very unlikely that there is no significant overall survival advantage of entrectinib over platinum-

clinically plausible (figures 1 & 2 and tables A & B in issue 4)?	pemetrexed chemotherapy in the ROS1 NSCLC population and we have some concerns about the plausibility of the comparator data. Please see further comments below (Issue 4).
Issue 4: OS and PFS modelling	
4. What approach to estimating PEM+PLAT overall survival (OS) and progression free survival (PFS) is appropriate for decision making (figure 4 & 5)? • ERG's preferred approach: hazard ratios (HRs) from an indirect comparison of entrectinib with PEM+PLAT using data from ASCEND-4 (with maintenance therapy) to estimate PEM+PLAT curve. • Company's preferred approach: HRs from an indirect comparison of entrectinib with crizotinib using data from PROFILE 1001, and applying HRs comparing crizotinib with PEM+PLAT (without maintenance therapy) from PROFILE 1014 to the estimated crizotinib curve to model PEM+PLAT.	The use of data from ASCEND-4, in principle, is the most appropriate comparator as this study included maintenance pemetrexed. However, the data from both datasets are not fully representative when considering platinum-pemetrexed (with maintenance pemetrexed) as first-line therapy. The randomised controlled PARAMOUNT study (Paz-Ares, JCO 2013) investigated the use of maintenance pemetrexed versus placebo following induction cisplatin-pemetrexed in patients with non-squamous NSCLC (unselected patient group). The OS for the maintenance pemetrexed arm was 17 months compared with 14 months for the placebo group. The median OS of PEM+PLAT in ASCEND-4 of 26.6 months is, therefore, higher than expected and is inevitably due to the crossover of patients on to ceritinib in this study. Thus, using these data as a comparator is likely over-estimating the survival of patients receiving PEM+PLAT. The impact of ALK as a prognostic factor in these data (compared with the unselected patient group in PARAMOUNT) is uncertain. Equally, the median OS of 10.8 months in PROFILE 1014 seems low, even accounting for the absence of maintenance pemetrexed. One would expect the OS in the comparator arm to be in the region of 12-14 months or potentially higher given the cross-over onto crizotinib.

	Neither dataset therefore seems fully representative of the expected OS figures. In addition, it is noted that less than a third of patients in the STARTRK2 study were first-line, the remainder receiving at least one prior line of therapy. The overall survival of patients in this dataset may therefore be underestimated compared with the first-line population in the proposed comparator groups. Furthermore, a significant proportion of patients in the STARTRK2 study had brain metastases (generally associated with worse prognosis) which may further underestimate the OS advantage of entrectinib compared with the comparator studies. Taking all these limitations into account we accept there is no available ideal comparator dataset. PARAMOUNT data could be taken into consideration for the expected OS in an unselected population. On balance, irrespective of the absolute figures, a survival gain of median [redacted] months (ERG approach) or median [redacted] months (company approach) both seem plausible and the true figure may lie between the two. If considering mean OS, a survival gain of [redacted] months (ERG approach) seems slightly more likely than a survival advantage of [redacted] months (company approach) but both may be plausible.
Issue 5: End-of-Life	
5a. What is the mean survival of people with advanced ROS1-positive NSCLC who are treated with PEM+PLAT induction followed with pemetrexed maintenance treatment?	Within the available literature, the data that most closely addresses this question are in a Korean population showing median OS of 20 months.
5b. Is it plausible that entrectinib will increase the survival of people with advanced ROS1-positive	Yes.

NSCLC compared with PEM+PLAT induction followed with pemetrexed maintenance treatment by at least 3 months?	
Issue 6: Pemetrexed maintenance therapy	
6a. What is the average duration of maintenance therapy with pemetrexed?	It is generally the better performance status patients that are offered maintenance pemetrexed thus there is an element of selection bias in terms of predicting how long patients may be on treatment. Generally, we could consider the average number of cycles to be more likely 6 than 8.
6b. Is assuming 8 cycles of maintenance therapy after 4 cycles of induction as used in the ERG scenario based on ASCEND-4 trial appropriate?	Four cycles of induction chemotherapy is standard practice. Average duration of maintenance pemetrexed is estimated above.
Issue 7: Subsequent treatments	
7a. Do you consider that all people with advanced ROS1-positive NSCLC who have discontinued first line-treatment would be given subsequent treatments?	No. Some patients will deteriorate quickly following or during first-line treatment and will not be well enough to consider further lines of therapy. We would estimate that approximately 60-70% patients would receive a subsequent line of therapy.
7b. Do you consider that PEM+PLAT would be the second-line treatment after entrectinib?	Yes
7c. Do you consider that atezolizumab (TA584) should be included in the cost of subsequent treatments?	In general, patients with driver genetic alterations do not tend to benefit from immunotherapy and there is also associated higher toxicity in these patients, perhaps due to exposure to prior TKIs. It would, therefore, be reasonable not to include atezolizumab in the cost of subsequent treatments.

Issue 8: Utilities	
8. Do you consider the ERG's or the company's utility values more appropriate? • ERG: utility values accepted in TA529 (PFS=0.81 and PPS=0.66) • Company: PFS utility estimated from STARTRK-2 (0.73) and PPS utility value from TA529 (0.66).	
Issue 9 Health care cost	
9. From looking at table E, is the ERG's or the company's approach to resource use for the PFS and PPS health states more appropriate?	The ERG's approach is probably more appropriate although it should be noted that CXR's are likely to be performed once per month or at least every other month for this patient group.
Issue 10: Cancer Drugs Fund	
10a. Does entrectinib meet the criteria for inclusion in the Cancer Drugs Fund? • Does entrectinib has plausible potential to be cost-effective? • Could data collection reduce the outstanding uncertainty identified in this report?	
10b. What data would be most useful to collect to address the outstanding uncertainties?	• Clinical outcomes – overall response rate, progression-free survival, overall survival • Duration of therapy/number of cycles • Subsequent therapies received

	• CNS activity - we would encourage inclusion of patients with active brain metastases. The compound is known to have CNS penetration and response in the brain can lead to considerable improvement in quality of life. This potential benefit has not been captured within the modelling of the technology appraisal and should be considered. It will be important to collect these data on CNS response and PFS if access to the drug is approved on the CDF.

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

Matching Adjusted Indirect Comparison for ROS1

A MAIC using the STARTRK-2 ROS1 efficacy population with EMA **D180 data cut (CCOD May 1, 2019 and ECOD 30 Nov 2017)** and the PROFILE 1001 Crizotinib data from Shaw et al. 2019 has been conducted.

For the comparison of entrectinib with crizotinib, the baseline characteristics selected for matching as per the original submission were sex, ECOG (0 or 1 vs 2), smoking history, prior treatments (treatment naïve vs prior treatment), age and Asian population. The original and weighted patient characteristics are summarised in Table 1.

For the comparison of entrectinib with Pemetrexed + platinum + pemetrexed maintenance, the baseline characteristics selected for matching as per the original submission were sex, ECOG (0 or 1 vs 2), smoking history, age, disease stage and Asian population. The original and weighted patient characteristics are summarised in Table 2.

Table 1. Baseline characteristics included in estimation of MAIC weights for comparison of entrectinib versus PROFILE 1001 crizotinib

	ESS	%(Asian)	Age Mean	%(ECOG 2)	%(Treatment naive)	%(Female)	%(Never smoke)
Crizotinib	53	39.6	55.0	1.9	13.2	56.6	75.5
Entrectinib original	78	46.2	53.3	12.8	26.9	62.8	56.4
Entrectinib reweighted	48.1	39.6	55.0	1.9	13.2	56.6	75.5

Table 2. Baseline characteristics included in estimation of MAIC weights for comparison of entrectinib versus ACEND4

	ESS	%(Asian)	Age Mean	%(ECOG 2)	%(Female)	%(Never smoke)	%(Stage IIIB)
Chemotherapy	53	43.9	54.0	5.9	61.0	65.2	2.7
Entrectinib original	78	46.2	53.3	12.8	62.8	56.4	1.3
Entrectinib reweighted	69.5	43.9	54.0	5.9	61.0	65.2	2.7

In the following tables, the results for OS, PFS BICR, PFS IA for Crizotinib and ASCEND4 are presented.

PROFILE 1001 – OS

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Crizotinib	Original	53	27	51.5 (30.37, NA)	
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	58.6	[redacted]	[redacted]	[redacted]

PROFILE 1001 – PFS BICR

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Crizotinib	Original	53	36	19.33 (15.27, 40.37)	
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	58.6	[redacted]	[redacted]	[redacted]

PROFILE 1001 – PFS IA

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Crizotinib	Original	53	36	19.33 (15.27, 40.37)	
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	58.6	[redacted]	[redacted]	[redacted]

ASCEND4 – OS

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Chemotherapy	Original	187	59	26.26 (22.84, NA)	
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	73.3	[redacted]	[redacted]	[redacted]

ASCEND4 – PFS BICR

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Chemotherapy	Original	187	117	7.99 (5.7, 11.13)	

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	73.3	[redacted]	[redacted]	[redacted]

ASCEND4 – PFS IA

Treatment	Scenario	n Patients	n Events	Median 95% CI	Hazard Ratio (95% CI)
Chemotherapy	Original	187	117	7.99 (5.7, 11.13)	
Entrectinib	Original	78	[redacted]	[redacted]	[redacted]
Entrectinib	Reweighted	73.3	[redacted]	[redacted]	[redacted]

Table 2: Overall efficacy by BICR in STARTRK-2 patients with ROS1-positive NSCLC, Data Cut D180 (ECOD: 30 Nov 2017, CCOD: CCOD May 1, 2019)

Efficacy Endpoint	**Entrectinib N= 78**
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
Objective Response Rate Number of Responses ORR% (95% CI) Complete Response, n (%) Partial Response, n (%)	[redacted]
Duration of Response* Number (%) of patients with events Median, months (95% CI) 6-month durable response % (95% CI) 9-month durable response % (95% CI) 12-month durable response % (95% CI)	[redacted]
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
PFS* Number (%) of patients with events Median, months (95% CI)	[redacted]
Time to CNS Progression	
Number (%) of patients with events	[redacted]
Median, months (95% CI)	[redacted]
Overall Survival	
Number (%) of patients with events	[redacted]
Median, months (95% CI)	[redacted]
NE= not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method. *Median and percentiles based on Kaplan-Meier estimates	

Table 3: Intracranial efficacy in STARTRK-2 ROS1-positive NSCLC patients with CNS disease at baseline by BICR, Data Cut D180 (ECOD: 30 Nov 2017, CCOD: CCOD May 1, 2019)

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by BICR)** **Measurable disease** **N=16**
IC-ORR Responders IC-ORR% (95% CI) Complete Response n (%) Partial Response n (%)	[redacted]
IC-DOR Number of patients with events (%) Median, months (95%)	[redacted]
IC-PFS Number of patients with events (%) Median, months (95% CI)	[redacted]
NE= not estimable. IC-ORR derived using RECIST 1.1 criteria applied only to CNS lesions. *Confidence Intervals (CI) calculated using the Clopper-Pearson method.	

Table 4: Summary of ROS1 efficacy results

	Company's integrated analysis (n = 53)	**ERG's preferred analysis (n = 78)**	**ERG's preferred analysis (n = 78)**
CCOD for enrolment	**30 Oct 2018**	**31 May 2018**	**1 May 2019**
Primary endpoints			
Objective response (CR or PR confirmed at repeat readings at least 28 days apart)			
Patients with response, n (%)	[redacted]	[redacted]	[redacted]
95% CI for response	[redacted]	[redacted]	[redacted]
Best objective response rate, n (%)			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Duration of response[d]			
Median months (95% CI)	[redacted]	[redacted]	[redacted]
Secondary endpoints			
Progression-free survival			
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]
Overall survival			
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]	[redacted]

Table 5: Modelled PFS, PPS and OS (undiscounted) using STARTRK-2 subgroup (n=78) – ERG preferred approach

	Previous ERG/technical team model results (ID1541 entrectinib ERG model post FAC corrected v0.3)		D180 model results (ID1541 entrectinib ERG model post FAC, D180 data, 15.11.19)	
ICER vs PEM+PLAT	£36,728		£33,749	
	Entrectinib	**PEM+PLAT**	**Entrectinib**	**PEM+PLAT**
Mean OS	[redacted]	39.21	[redacted]	38.12
Mean PFS	[redacted]	11.43	[redacted]	11.87
Mean PPS	[redacted]	27.78	[redacted]	26.25
Mean ToT	[redacted]	11.60	[redacted]	12.04
Mean number of cycles	[redacted]	11.43	[redacted]	11.87

Table 2: Modelled PFS, PPS and OS (undiscounted) using STARTRK-2 subgroup (n=78) – Roche preferred approach

	Previous ERG/technical team model results (ID1541 entrectinib ERG model post FAC corrected v0.3)		D180 model results (ID1541 entrectinib ERG model post FAC, D180 data, 15.11.19)	
ICER vs PEM+PLAT	£21,470		£21,023	
	Entrectinib	**PEM+PLAT**	**Entrectinib**	**PEM+PLAT**
Mean OS	[redacted]	20.16	[redacted]	20.17
Mean PFS	[redacted]	9.91	[redacted]	10.85
Mean PPS	[redacted]	10.25	[redacted]	9.33
Mean ToT	[redacted]	10.06	[redacted]	11.00
Mean number of cycles	[redacted]	9.91	[redacted]	10.85

BMJ TAG

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

ERG review of company's response to technical engagement report

Source of funding

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129317

1 Summary

This document provides the Evidence Review Group's (ERG's) critique of the company's response to technical engagement for the single technology appraisal (STA) of entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer (hereafter ROS1+ NSCLC). The company submitted a response to each issue set out in the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) and the ERG had provided its critique in the same format.

The company expressed agreement with some of the NICE technical team's preferences which differed from their original submission – including the population on which clinical data are based in the model and the utility values and resource use assumptions for progression-free survival (PFS) and post-progression survival (PPS) – but did not submit an updated base case. The company provided scenario analyses requested by NICE, using the NICE technical team's base case, to assess the impact of the duration of pemetrexed maintenance therapy and the proportion of patients receiving subsequent treatments on cost-effectiveness (Section **Error! Reference source not found.**).

2 ERG review of issues

2.1 Issue 1: Comparators

The company agreed with the NICE technical team that pemetrexed in combination with platinum chemotherapy (PEM+PLAT) is the key comparator for entrectinib in this single technical appraisal (STA). The ERG acknowledges that crizotinib is only available for patients with ROS1+ NSCLC through the Cancer Drugs Fund (CDF), and is therefore ineligible for consideration as a comparator in an STA in line with NICE's position statement. However, the ERG heard consistently from clinical experts that crizotinib should be considered the key comparator for entrectinib (Section 3.3 of the ERG report), which was also highlighted by the company in its initial submission and the response to technical engagement. As such, the ERG considers the comparator considered in this appraisal (PEM+PLAT) to be incoherent with what is currently considered standard of care (crizotinib).

2.2 Issue 2: Population

In their response, the company agreed to proceed with the ERG's preferred efficacy population, which is based on patients with ROS1-inhibitor naïve ROS1+ NSCLC and measurable disease at baseline from STARTRK-2 (n = 78). The company reiterated that their integrated ROS1+ NSCLC efficacy set from the ALFA, STARTRK-1 and STARTRK-2 studies (n = 58) was prespecified and has been accepted by regulators, although the ERG notes from the company's response to clarification that the European Medicines Agency [redacted]. The company acknowledges that the ERG's preferred efficacy set offers benefits because STARTRK-2 was the only study designed to assess efficacy and use prospective tumour scan assessments, and all patients received entrectinib in line with its proposed marketing authorisation.

The ERG notes that the 12-month minimum follow-up restriction recommended by the United States Food and Drug Administration (FDA) for the company's primary efficacy set was based on the assessment of durability of response, an outcome which is not reflected in the economic model. The company acknowledges that including patients with less than 12 months' follow-up means that more patients can contribute useful data up to the point at which they are censored for outcomes reflected in the economic model (OS and PFS).

The ERG accepts the company's point that overall survival (OS) is immature regardless of the population used but OS and progression-free survival (PFS) based on the ERG's preferred efficacy set are likely to be more reliable because they include a higher number of patients and events. The extent

of difference between the ERG's and company's preferred efficacy sets varies by outcome but the direction of difference is consistent, with the company's results being more favourable to entrectinib.

2.3 Issue 3 and Issue 4: Indirect comparison of entrectinib versus pemetrexed

The company acknowledges the limitations of using evidence for patients with ALK+ NSCLC as a proxy, and the ERG agree that no alternative evidence exists in a ROS1+ NSCLC population to estimate the relative effectiveness of entrectinib and PEM+PLAT. While there is a precedent for using evidence from ALK+ NSCLC as a proxy for ROS1+ NSCLC (NICE TA529) and the two populations share similarities (e.g. younger age, non-smoker or light smoking, adenocarcinoma histologic type), uncertainty pertaining to absolute and relative treatment effects between the two cannot be resolved.

The company and the ERG agree that both options for an indirect comparison of entrectinib vs PEM+PLAT have significant limitations but disagree about which is likely to provide the most reliable estimates. As described in the ERG report, the ERG considers the methodological limitations of the company's approach more serious, namely the method used to adjust OS for crossover in PROFILE 1014 and non-proportional hazards for PFS, meaning neither hazard ratio (HR) from the study is fit for decision-making (Table 1).

The company argue that the ERG's preferred approach, "hugely overestimates the survival benefits of PEM+PLAT due to the high use of ALK inhibitors after progression", due to 42.7% crossover from PEM+PLAT to ceritinib in ASCEND-4 (and 51.6% receiving any ALK-inhibitor). The ERG acknowledges that subsequent treatments received in trials (due to crossover or otherwise) often do not reflect clinical practice in a given context and can lead to an overestimation of OS. In this case, clinical experts advised that a 60–70% of patients would receive subsequent therapies that would be expected to extend life after PEM+PLAT (with associated costs, see Issue 7), and so the ERG does not consider it likely that the *absolute* estimate of OS with PEM+PLAT will be "hugely overestimated" due to post-progression targeted therapy use in ASCEND-4. However, the ERG acknowledges that ceritinib would not be an option for patients with ROS1+ NSCLC in UK clinical practice, and the *relative* treatment effect for OS may be biased in favour of PEM+PLAT because a [redacted] proportion of patients received subsequent anti-cancer treatments after entrectinib ([redacted] in the company's efficacy set and [redacted] in the ERG's efficacy set; ERG report, Section 5.3.8.7).

Table 1. Comparison of the two approaches for the indirect comparison of entrectinib vs PEM+PLAT

	ERG preferred (ASCEND-4 MAIC)	Company preferred (PROFILE 1014 HRs)
Method	MAIC of ERG's preferred entrectinib ROS1 population vs PEM+PLAT for ALK+ from ASCEND-4	PROFILE 1014 HRs (crizotinib vs PEM+PLAT) applied to the estimated crizotinib curve obtained through a separate MAIC HR using PROFILE 1001
Key assumption(s)	1) Absolute effect of PEM+PLAT is the same for ALK+ and ROS1+ NSCLC	1) Relative effect of crizotinib vs PEM+PLAT is the same for ALK+ and ROS1+ NSCLC 2) PROFILE 1001 MAIC is a sound basis for estimating the crizotinib curves and applying the PROFILE 1014 HRs
Prior treatment	Both recruited untreated populations which may favour PEM+PLAT	
Study design	Both are multicentre, open-label, RCTs	
Pemetrexed maintenance	Yes, as per UK clinical practice	No, doesn't reflect UK clinical practice and may favour entrectinib
Extent of crossover	46% (to ceritinib)	84% (to crizotinib)
Crossover adjustment	None, likely to favour PEM+PLAT	Yes, but flawed. The ERG is TA529 deemed the adjustment method unfit for purpose and preferred using unadjusted OS (at 19% crossover at the time of TA529).
Proportional hazards	Not assessed	HRs are the basis of the company's method and this key assumption does not hold for PFS
Possible confounding factors	Prior treatment and crossover to ceritinib may overestimate PEM+PLAT relative to entrectinib.	Of applying PROFILE 1014 HRs: unlikely as retains randomisation between crizotinib and PEM+PLAT. Of PROFILE 1001 MAIC: disease stage/ brain metastases - unknown direction.
Modelled OS and PFS (months, undiscounted; using ERG's preferred efficacy set)	Entrectinib vs PEM+PLAT Mean OS: [redacted] vs 39.2 ([redacted] gain) Mean PFS: [redacted] vs 11.4 ([redacted] gain)	Entrectinib vs PEM+PLAT Mean OS: [redacted] vs 15.6 ([redacted] gain) Mean PFS: [redacted] vs 11.7 ([redacted] gain)

Abbreviations: HR, hazard ratio; NSCLC, non-small-cell lung cancer; PEM+PLAT, pemetrexed plus platinum chemotherapy; RCT, randomised controlled trial; RoB, risk of bias.

The ERG agrees that mean OS with PEM+PLAT estimated by its preferred approach ([redacted] months) is longer than would be expected in clinical practice and is longer than the mean OS estimated in the appraisal of crizotinib for ROS1+ NSCLC (17.6 months). However, the ERG highlights that absolute OS in clinical trials is often much longer than observed in clinical practice due to factors such as more frequent scans, patient selection and subsequent therapies, which has been shown for crizotinib in ROS1+ NSCLC (median OS in PROFILE 1001 of 51.4 months compared with 18.5 months in the US Flatiron registry; see company's submission, Appendix D.5). Furthermore, the ERG points to the possibility that OS for entrectinib is also overestimated in the model, with a mean OS of [redacted] months. Notwithstanding the potential bias introduced by the subsequent therapy imbalance for PEM+PLAT and entrectinib in the ERG's approach, the ERG considers the survival *gains* rather than the absolute estimates more realistic and conservative with the ERG approach ([redacted] months) than the company's approach ([redacted] months), and more in line with clinical expert opinion cited in the company's response

(expected 12 to 24-month OS gain) and with the conclusions in TA529 that the maximum expected survival benefit of crizotinib vs PEM+PLAT would be between 13 and 16 months. The ERG also notes that the results of both MAICs conducted for entrectinib vs crizotinib and entrectinib vs PEM+PLAT have shown non-statistically significant differences is OS across treatments.

2.4 Issue 5: End of life

The ERG agrees that entrectinib meets the first criteria regarding extension to life of at least three months compared with PEM+PLAT in the company's and the ERG's base case (undiscounted mean OS gains of [redacted] months and [redacted] months, respectively).

The ERG considers the second criteria of survival less than 24 months more contentious. The company state that clinical experts expect survival to be less than 24 months with PEM+PLAT and considered the estimates from the company's base case ([redacted] months) and ERG base case ([redacted] months) to be unrealistic in opposite directions. The ERG considers the relative effect of entrectinib vs PEM+PLAT in its own base case more realistic than the substantial survival gain estimated by the company's base case but accepts that the absolute OS estimates for entrectinib and PEM+PLAT to overestimate OS in clinical practice, as is often the case in clinical trials. As such, the ERG agrees that the end of life criteria is likely to be met when based on expected survival in clinical practice, but mean OS could be longer than 24 months depending on the chosen method of modelling OS from clinical trials.

2.5 Issue 6: Pemetrexed maintenance therapy

The company argue that clinical expert opinion suggested that it is unlikely for patients to receive 8 cycles of maintenance therapy after induction treatment. The ERG notes that duration of maintenance therapy is one of the key drivers of the economic model and that clinical expert opinion provided to the ERG was that the duration of maintenance treatment can vary substantially.

The ERG agrees with the company that changing the duration of maintenance treatment in the model is only a costing exercise and does not adjust for treatment effectiveness of maintenance therapy. However, the ERG notes that the only approach that considers the clinical effectiveness of maintenance therapy in the economic analysis is the ERG's preferred approach of using ASCEND-4 MAIC (as the company's preferred PROFILE 1014 study did not include maintenance treatment).

Given the impossibility of adjusting treatment effectiveness according to the duration of pemetrexed's maintenance therapy, the ERG considers that including different scenarios around the

cost of maintenance therapy is valuable (and often used in NICE's technology assessments). Results of the ERG's scenarios analysis are reported in Section 3.

2.6 Issue 7: Subsequent treatments

During the technical engagement call it was discussed by clinical experts that it is unrealistic to assume that 100% of patients who have discontinued first line treatment would receive subsequent treatment, and that a more realistic proportion would be around 60% or 70% of patients. Therefore, the company performed scenario analyses accordingly. The company also note that in these scenarios the proportion who received subsequent therapy after receiving PEM+PLAT was set to equal the proportion who received subsequent treatment after entrectinib.

The ERG reviewed the company's implementation of these scenarios in the model and agrees with the company's approach, however notes that the company assumed that 60.5% of patients receive subsequent therapy (in the 60% scenario). The impact of correcting this in the model was minimal. The ERG also notes that for the scenario analysis where entrectinib patients are assumed to receive only PEM+PLAT as a subsequent therapy, the assumption in the model was still that 100% of patients receive PEM+PLAT.

The ERG changed the proportion of patients from 60.5% to 60% and conducted scenario analyses assuming that 60% or 70% of patients in the model receive subsequent treatment. The ERG also conducted additional scenario analysis where either 60% or 70% of entrectinib patients were assumed to receive only PEM+PLAT after initial treatment with entrectinib. Results are presented in Section 3.

2.7 Issue 8: Utilities

The company accepted that the ERG's approach of using one data source to inform health state utilities is preferable.

2.8 Issue 9: Health care cost

The company agreed that the ERG's approach to resource use for the PFS and PPS health states is more appropriate than their original approach based on TA529.

2.9 Issue 10: Cancer Drugs Fund

The company proposes that entrectinib is a candidate for entry into the CDF because:

- there are clinical- and cost-effectiveness uncertainties due to the limited and immature data;
- their base case and that of the NICE technical team produce ICERs versus PEM+PLAT that fall under the maximum end-of life threshold;
- longer-term, comparative data in a larger number of patients with ROS1+ NSCLC would reduce the current uncertainty in the economic evaluation.

The company outlines various sources of additional data that may reduce uncertainty including updated data from STARTRK-1 and STARTRK-2, details of which will be confirmed as soon as possible, and ongoing real-world data collection via patient registries. The company states that data collected by Public Health England (PHE) during a CDF period would help to address the current uncertainties and that they intend to collaborate closely with NICE, NHS England and PHE to determine how this would best be done.

The ERG notes that [redacted].

3 Additional analysis undertaken by the ERG

Table 2 reports the results of the ERG's additional analysis for the comparison of entrectinib with PEM+PLAT. The key driver of the economic results remains the method used to estimate treatment effectiveness for PEM+PLAT, followed by the duration of maintenance treatment assumed for pemetrexed. Depending on the assumptions used to estimate the cumulative ICER, the ERG's results vary from £37,910 to £42,572 per QALY gained for entrectinib vs PEM+PLAT.

For the comparison of entrectinib vs crizotinib and when it is assumed that PFS and OS HR=1 (please see ERG report for more details), the total entrectinib costs amount to:

1. Including assumptions 1; 4; 6; 8; 9 in Table 1: £[redacted] vs £120,269 for crizotinib (regardless of treatment duration with pemetrexed);
2. Including assumptions 1; 5; 7; 8; 9 in Table 1: £[redacted] vs £119,972 for crizotinib (regardless of treatment duration with pemetrexed).

With this difference in costs, crizotinib's list price would have to be reduced by [redacted] to yield the same total cost in the economic analysis as entrectinib (in both scenarios).

Table 2. ERG's additional analysis

Description	Issue (in technical engagement report)	ICER
Company's base case using company's analysis set	-	£15,628
Company's base case using company's analysis set with errors corrected by the ERG	-	£16,139
Company's corrected base case using ERG's preferred efficacy set	Issue 2	£21,845
ERG scenarios		
1 Removing cost of ROS1 testing	-	£19,566
2 Using the ASCEND-4 MAIC HRs to estimate OS and PFS for PEM+PLAT and changing the duration of induction treatment with PEM from 6 to 4 cycles to match the duration of induction treatment with PEM in ASCEND-4	Issue 4	£52,399
3 Assuming maintenance treatment with pemetrexed after cisplatin and carboplatin for 4,6 and 8 cycles	Issue 6	£19,638
		£18,754
		£18,351
4 Assuming that 60% of patients who discontinued first-line treatment receive subsequent treatments	Issue 7	£21,538
5 Assuming that 70% of patients who discontinued first-line treatment receive subsequent treatments	Issue 7	£21,603
6 Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib assuming 60% of patients receive subsequent treatment	Issue 7	£25,375
7 Applying PEM+PLAT as the subsequent treatment for all patients who progress on entrectinib assuming 70% of patients receive subsequent treatment	Issue 7	£25,534
8 Using TA529-accepted utility values of 0.81 for PFS and 0.66 for PPS	Issue 8	£21,232
9 Using the ERG's clinical expert's suggested resource for PFS and PPS states	Issue 9	£22,812
Cumulative impact of ERG's assumptions (1; 2; 4; 6; 8; 9)		
3 Assuming maintenance treatment with pemetrexed after cisplatin and carboplatin for 4,6 and 8 cycles	Issue 6	£42,572
		£40,279
		£38,304
Cumulative impact of ERG's assumptions (1; 2; 5; 7; 8; 9)		
3 Assuming maintenance treatment with pemetrexed after cisplatin and carboplatin for 4,6 and 8 cycles	Issue 6	£42,179
		£39,885
		£37,910

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; OS, overall survival; PEM, pemetrexed; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival; PPS, post-progression survival.

BMJ TAG

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer [ID1541]

ERG review of updated data provided by the company

Source of funding

This report was commissioned by the NIHR Systematic Reviews Programme as part of project number 129317

1 ERG review of the updated data

The company submitted updated clinical effectiveness results on Friday 15 November in support of entrectinib for advanced ROS1-fusion positive non-small-cell lung cancer (ROS1+ NSCLC), which were presented at the appraisal committee meeting (ACM) on 20 November 2019. The company also submitted updated matching adjusted indirect comparisons (MAICs) of entrectinib versus crizotinib and entrectinib versus pemetrexed plus platinum chemotherapy (PEM+PLAT), a new version of the economic model, and an updated summary of project characteristics (SmPC). This document provides a critique and validation of the new clinical effectiveness results, MAIC results and associated incremental cost-effectiveness ratios (ICERs).

1.1 Marketing authorisation and indication

The updated SmPC provided by the company confirms that entrectinib will marketed under the name Rozlytrek™ for the treatment of adult patients with ROS1+ advanced NSCLC not previously treated with ROS1 inhibitors. The SmPC recommends entrectinib be started at a dose of 600 mg once daily (except for patients with special precautions) until disease progression or unacceptable toxicity, which is how the drug was given in the STARTRK-2 study. At the time of writing, entrectinib has not yet been granted marketing authorisation from the European Medicines Agency (EMA).

The updated SmPC includes updated special warnings and precautions and updated efficacy results from an integrated efficacy set of [redacted] patients, whereas the ERG and NICE technical team deemed the ROS1+ NSCLC population from STARTRK-2 (n = 78) more suitable for decision-making.

1.2 Updated data cut for entrectinib

Documents submitted by the company state that the updated data are from analyses with a clinical cut-off date (CCOD) of 1 May 2019 and an "ECOD" of 30 November 2017. ECOD is not defined but if it refers to an enrolment cut-off date, the ERG notes that this is inconsistent with the enrolment cut-off dates stated in the original submission (31 May 2018 for the 31 July 2018 CCOD and 21 December 2018 for the 30 October 2018 CCOD; Table 6 of the ERG report). Nonetheless, the number of patients included in the updated analyses is the same as the ERG and technical team's preferred efficacy set (n = 78), which includes patients with ROS1-inhibitor naïve ROS1+ NSCLC in STARTRK-2 (Table 1).

The updated results for overall survival (OS) and progression-free survival (PFS) are very similar to those included in the ERG's base case (Table 1). [redacted] additional patients have died since the last data cut and median OS has stayed at [redacted]. The updated PFS analysis includes [redacted] additional

events and median PFS has increased slightly to [redacted]) since the analysis underpinning the ERG's base case ([redacted]).

Table 1. Comparison of the ERG's preferred results for entrectinib and results from the updated data-cut (1 May 2019)

	ERG/technical team results	Company's updated results
Entrectinib population	STARTRK-2 (n = 78) ROS1+ NSCLC, measurable disease at baseline, no prior ROS1 inhibitor, no minimum follow-up	
Entrectinib CCOD	31 May 2018	1 May 2019
Overall survival		
Patients with events, n (%)	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]
Progression-free survival (BICR)		
Patients with events, n (%)	[redacted]	[redacted]
Time to event (months), median (95% CI)	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CCOD, clinical cut-off date; ERG, evidence review group; OS, overall survival; PFS, progression-free survival.

The company also provided updated results for objective response rate (ORR), duration of response (DoR) and time to CNS progression, and intracranial efficacy outcomes for the subgroup of patients with CNS disease at baseline. The ERG has not reproduced the additional results because they were not used in the economic model but notes that all results are similar to those from the earlier data-cut. The ERG considers it reassuring that the updated results are consistent with those used in the ERG's base case given that the updated results reflect longer follow-up and a higher number of observed events for both key outcomes.

1.3 Updated MAIC of entrectinib versus PEM+PLAT

The 1 May 2019 data cut for entrectinib was used to conduct updated MAICs with the PEM+PLAT arm of the ASCEND-4 study (untreated ALK+ NSCLC), which was the ERG's preferred method of indirect comparison between entrectinib and PEM+PLAT. The company submitted updated tables showing patient characteristics before and after the entrectinib population were reweighted to match the population of ASCEND-4. Baseline characteristics used for matching were the same as the original submission and prior treatment could not be used for matching because there was too little overlap between the studies.

Updated results from the MAICs were presented for OS, PFS by BICR and PFS by IA, but the ERG has not reproduced the PFS by IA data because both the ERG and the company's base case used the BICR measurement. The ERG notes small changes in the hazard ratios (HRs) and respective confidence intervals (CIs) between the ERG's preferred results for OS and PFS and the updated results submitted

by the company. The reweighted HRs, which are the basis for estimating treatment effectiveness in the economic model, changed from [redacted] to [redacted] for OS and from [redacted] to [redacted] for PFS (Table 2).

Table 2. Comparison of the ERG's preferred MAIC of entrectinib vs PEM+PLAT and the company's updated analyses (both using the STARTRK-2 subgroup and PEM+PLAT data from ASCEND-4)

	ERG/technical team results (CCOD 31 May 2018)	Company's updated MAIC (CCOD 1 May 2019)
OS, median months (95% CI)		
PEM+PLAT	26.26 (22.84, NE)	26.26 (22.84, NE)
Entrectinib original	[redacted]	[redacted]
Entrectinib reweighted	[redacted]	[redacted]
Unweighted HR (95% CI)	[redacted]	[redacted]
Reweighted HR (95% CI)	[redacted]	[redacted]
PFS by BICR, median months (95% CI)		
PEM+PLAT	7.99 (5.7, 11.13)	7.99 (5.7, 11.13)
Entrectinib original	[redacted]	[redacted]
Entrectinib reweighted	[redacted]	[redacted]
Unweighted HR (95% CI)	[redacted]	[redacted]
Reweighted HR (95% CI)	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CCOD, clinical cut-off date; ERG, evidence review group; IA, investigator assessment; OS, overall survival; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival.

1.4 Updated MAIC of entrectinib versus crizotinib

The NICE technical report concluded that PEM+PLAT is the most appropriate comparator for entrectinib because crizotinib is only available through the Cancer Drugs Fund (CDF). The company nevertheless provided updated results from MAICs of entrectinib vs crizotinib using the 1 May 2019 entrectinib data cut (ERG's preferred STARTRK-2 subgroup) and 2019 data from the single-arm PROFILE 1001 study of crizotinib (Shaw 2019).

Updated tables submitted by the company show that the entrectinib population was successfully reweighted for the chosen characteristics to match the population of PROFILE 1001. However, disease stage and the presence of metastases in the central nervous system (CNS) could remain a key confounder in the analysis because baseline data were not available for PROFILE 1001. Comparison of the ERG's results and the updated analyses show some movement in the HR point estimates but none of the results show statistically significant differences between treatments (Table 3).

Table 3. Comparison of the ERG's preferred MAIC of entrectinib vs crizotinib and the company's updated analyses (both using the STARTRK-2 subgroup and PROFILE 1001 data from Shaw 2019)

	ERG/technical team results (CCOD 31 May 2018)	Company's updated MAIC (CCOD 1 May 2019)
OS, median months (95% CI)		
Crizotinib	51.5 (30.37, NE)	51.5 (30.37, NE)
Entrectinib original	[redacted]	[redacted]
Entrectinib reweighted	[redacted]	[redacted]
Unweighted HR (95% CI)	[redacted]	[redacted]
Reweighted HR (95% CI)	[redacted]	[redacted]
PFS by BICR, median months (95% CI)		
Crizotinib	19.33 (15.27, 40.37)	19.33 (15.27, 40.37)
Entrectinib original	[redacted]	[redacted]
Entrectinib reweighted	[redacted]	[redacted]
Unweighted HR (95% CI)	[redacted]	[redacted]
Reweighted HR (95% CI)	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CCOD, clinical cut-off date; ERG, evidence review group; OS, overall survival; PFS, progression-free survival.

1.5 Updated ICER validation

The company submitted an updated model from which a new ICER for entrectinib versus PEM+PLAT was derived (Table 4). The company reported a reduction in the ICER from £36,728 to £33,749 when results from the updated ASCEND-4 MAIC are used to model treatment effectiveness.

The ERG investigated the company's updated model and noted that the fitted curves for entrectinib differed from the ones used in the company's original model. The ERG assumes that this results from updated KM curves being used, which might have led to a new curve fitting exercise, although the company did not provide the updated KM curves or details of a new curve fitting exercise. Therefore, the ERG could not replicate the company's updated results in the previously available model but notes that the updated model providing the £33,749 ICER seems to include the updated hazard ratios.

Table 4. Modelled PFS, PPS and OS (undiscounted) using the STARTRK-2 subgroup (n = 78) and the ERG's preferred method of indirect comparison (ASCEND-4 MAIC)

Results	ERG/technical team results		Updated data cut (CCOD 1 May 2019)	
Model version	**ID1541 entrectinib ERG model post FAC corrected v0.3**		**ID1541 entrectinib ERG model post FAC, D180 data, 15.11.19**	
ICER vs PEM+PLAT	£36,728		£33,749	
	Entrectinib	PEM+PLAT	Entrectinib	PEM+PLAT
Mean OS	[redacted]	39.21	[redacted]	38.12
Mean PFS	[redacted]	11.43	[redacted]	11.87
Mean PPS	[redacted]	27.78	[redacted]	26.25

Abbreviations: CCOD, clinical cut-off date; ERG, evidence review group; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; OS, overall survival; PEM+PLAT, pemetrexed plus platinum therapy; PFS, progression-free survival; PPS, post-progression survival.