NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Pfizer:
   a. Full submission
   b. Additional information submission
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **NICE medicines optimisation team (MOT) report**

4. **Patient group, professional group, and NHS organisation submission** from:
   a. British Thoracic Oncology Group

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
   a. External Assessment Report
   b. EAG response to company additional information submission

   External Assessment Report – factual accuracy check: no factual inaccuracies identified.

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: cost-comparison

Crizotinib for treating ROS1-positive advanced non-small cell lung cancer (MA review of TA529) [ID6289]

Document B

Company evidence submission

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Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Description
AACR	American Association for Cancer Research
AE	Adverse event
AIC	Akaike information criterion
ALAT	Alanine aminotransferase
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
ASAT	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
ATE	Arterial thrombotic event
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BM	Brain metastases
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drug Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CGH	Comparative genomic hybridisation
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CLcr	Calculated creatinine clearance
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CNG	Copy number gain
CR	Complete response
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Congress
EMA	European Medicines Agency
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 lung-cancer quality of life questionnaire
EPAR	European public assessment report
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
FISH	Fluorescence *in situ* hybridization

Abbreviation	Description
H_0	Null hypothesis
H_A	Alternative hypothesis
HGFR	Hepatocyte growth factor receptor
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IASLC	International Association for The Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
KRAS	Kristen rat sarcoma viral oncogene
LOT	Line of therapy
MAIC	Matching adjusted indirect comparison
MET	Mesenchymal epithelial transition
MRI	Magnetic resonance imaging
NA	Not applicable
NDRS	National Data Registration System
NE	Not evaluable
NGS	Next-generation sequencing
NHS	National Health Services
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase gene fusion
ORR	Overall response rate
OS	Overall survival
OxOnc	Oxford Oncology
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PF	Prognostic factor
PFS	Progression-free survival
PICOS	Population, intervention, comparator, outcomes, study design
PR	Partial response
PROs	Patient reported outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
QoL	Quality of life
RCT	Randomized controlled trials
RECIST	Response Evaluation Criteria in Solid Tumours
ROBINS-I	Risk of Bias in Non-Randomized Studies – of Interventions
RON	Recepteur d'origine nantais
ROS1	Proto-oncogene tyrosine-protein kinase 1
RR	Response rate
RTK	Receptor tyrosine kinase

Abbreviation	Description
RT-PCR	Reverse transcriptase polymerase chain reaction
RWE	Real world evidence
SACT	Systemic Anti-cancer Therapy
SAE	Serious adverse event
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
STC	Simulated treatment comparison
TEAE	treatment-emergent adverse event
TEM	Treatment effect modifier
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TRAE	Treatment-related adverse event
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
TTR	Time to tumour response
ULN	Upper limit of normal
VTE	Venous thromboembolism
WCLC	World Conference on Lung Cancer

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. The final scope for crizotinib for the treatment of ROS1-positive advanced NSCLC was issued by the National Institute for Health and Care Excellence (NICE) in April 2024. A summary of the decision problem for crizotinib in ROS1-positive advanced NSCLC is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with ROS1-positive advanced non-small cell lung cancer	Adults with ROS1-positive advanced NSCLC	N/A
Intervention	Crizotinib	Crizotinib 250 mg	N/A
Comparator(s)	Entrectinib	Entrectinib	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse events of treatment • health-related quality of life	As per final scope: **Efficacy outcomes:** • overall survival • progression-free survival • response rates (overall response rate, partial response, duration of response, disease control rate) • Time to tumour response • Time-to-treatment failure • Disease-free survival rate **Safety and tolerability outcomes:** • adverse events (any grade, serious adverse events, treatment-related) • treatment switch or discontinuation due to adverse events **Health-related quality of life:** • Mean scores and change from baseline in patient reported outcome measures (EORTC QLQ-C-30, EORTC QLQ LC-13, EQ-5D)	N/A
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed	A cost-comparison appraisal has been carried out.	N/A

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	in terms of incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Special considerations including issues related to equity or equality	N/A	N/A	N/A

Abbreviations: AE, adverse events; ALK, anaplastic lymphoma kinase; BSC, best supportive care; NICE, National Institute for Health and Care Excellence; N/A, not applicable; NSCLC, non-small cell lung cancer; TRAEs: treatment-related adverse events; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs, and administration requirements associated with crizotinib for ROS1-positive advanced NSCLC is presented in Table 2. The summary of product characteristics (SmPC) and European public assessment report (EPAR) for crizotinib in this indication are presented in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Crizotinib (Xalkori®)
Mechanism of action	Crizotinib is a first-in-class, orally available, small-molecule, RTK inhibitor with selective, dose-dependent activity against ROS1 RTK and its oncogenic variants (e.g. ROS1 fusion proteins and selected ROS1 mutant variants). Crizotinib is also an inhibitor of the ALK RTK and its oncogenic variants (i.e. ALK fusion events and selected ALK mutations), HGFR (c-MET) and RON RTKs.[2,3]
Marketing authorisation/CE mark status	Crizotinib received a positive opinion from the CHMP on 21 July 2016 for the treatment of adults with ROS1-positive advanced NSCLC and received EU marketing authorisation for this indication on 25 August 2016.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• Xalkori® is indicated for the treatment of adults with ROS1-positive advanced NSCLC.[3] This licensed indication represents the indication detailed in this submission. Other indications include: • the first-line treatment of adults with ALK-positive advanced NSCLC.[4] • the treatment of adults with previously treated ALK-positive advanced NSCLC.[5] • the treatment of paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma. Crizotinib has the following contraindications: • Severe hepatic impairment • Hypersensitivity to crizotinib or excipients listed in the SmPC.[5]
Method of administration and dosage	Oral 250 mg twice daily (a total of 500 mg daily) for adult patients
Additional tests or investigations	ROS1-positivity must be confirmed prior to initiation of crizotinib. The National Genomic Test Directory for Cancer includes ROS1 testing in the regular workup of NSCLC.
List price and average cost of a course of treatment	List price: £4,689.00 for 1 pack 60 × 200 mg or 60 × 250 mg capsules.
Patient access scheme/commercial arrangement (if applicable)	A simple confidential discount patient access scheme of [redacted] has been submitted to the Department of Health for crizotinib in first-line ROS1-positive NSCLC.

Abbreviations: ALK, anaplastic lymphoma kinase; CHMP, Committee for Human Medicinal Products; EMA, European Medicines Agency; EU, European Union; HGFR, hepatocyte growth factor receptor; NSCLC, non-small cell lung cancer; PAS, patient access scheme; RON, recepteur d'origine nantais; RTK, receptor tyrosine kinase; SmPC, summary of product characteristics; UK, United Kingdom.

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

B.1.3.1 Disease overview

Lung cancer is broadly categorised as either small cell lung cancer or NSCLC, with the latter responsible for 80–85% of primary lung cancers in the UK.[6] NSCLC can be further subclassified predominantly into adenocarcinoma (~40% of cases), squamous cell carcinoma (~25–30% of cases), or large-cell carcinoma (~10–15% of cases).[7–9]. Annually in the UK over 48,000 people are diagnosed with lung cancer, accounting for approximately 13% of cancer diagnoses.[6]

Lung cancer patients typically present with symptoms including chronic cough, dyspnoea, haemoptysis, chest pain, recurrent chest infection, loss of appetite, and fatigue.[10] The National Optimal Lung Cancer Pathway from the National Health Service England (NHSE)[11] outlines imaging, biopsy, and histology procedures used for lung cancer diagnosis and staging, and the National Institute for Health and Care Excellence (NICE) provides advice for best practices. The current diagnostic standard of care includes molecular tests for specific oncogenic drivers performed at the time of diagnosis, including the use of next generation sequencing-based methodology.[12,13]

Genomic profiling has facilitated the use of targeted medicines for patients with oncogene-addicted NSCLC.[14] A rearrangement in the proto-oncogene tyrosine-protein kinase 1 gene (ROS1) is observed in ~1–2% of NSCLC cases, but is more common among young patients with no history of smoking.[15] Fusion of the gene segment encoding the ROS1 kinase domain to any of several catalogued partner genes results in the constitutive activation of ROS1-dependent signalling pathways, driving tumorigenesis.[16]

B.1.3.2 Clinical pathway of care

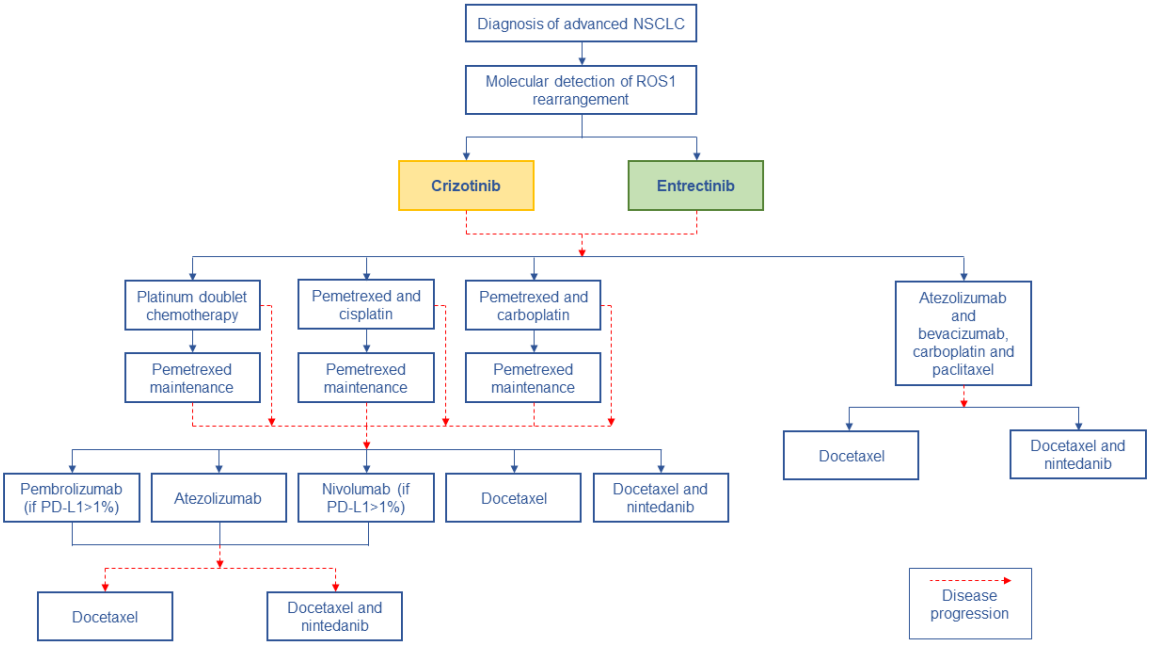
According to the current NICE clinical guideline for lung cancer (NG122), systemic NSCLC treatment pathways are based on the detection of targetable molecular markers.[17] Targetable markers with NICE treatment guidelines include mutations in ROS1, EGFR, ALK, RET, NTRK, KRAS, METex14, and BRAF, as well as the proportion of tumour cells expressing PD-L1. Next-generation sequencing panels and other molecular tests are routinely performed to detect mutations in each of these genes for non-squamous NSCLC.[18]

Patients with NSCLC positive for ROS1 mutation should receive targeted therapy in the initial treatment line prior to non-targeted therapies (Figure 1). Current NICE guidelines recommend either entrectinib or crizotinib as first-line therapies, with chemotherapy as a second-line treatment option.[2,17,19] Crizotinib use within the Cancer Drug Fund (CDF) is permitted based on adherence to the conditions of the managed

access agreement.[2] The recommendation includes patients who have or have not previously received cytotoxic chemotherapy for locally advanced or metastatic NSCLC.

Crizotinib is appropriate for first-line use as this provides crizotinib to patients who are most likely to respond to targeted ROS1 inhibition with the greatest clinical benefit early in the treatment pathway. ROS1-positive NSCLC status should normally be established prior to initiation of crizotinib therapy. The 2018 CDF 'Managed Access Agreement', states that NHSE has a strong preference for ROS1-positive patients to be treated with crizotinib as first-line therapy for advanced NSCLC but recognises that some patients have had to be treated with chemotherapy for urgent clinical reasons before the ROS1 result is known. Assessment of ROS1 status should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. An accurate and validated assay for ROS1 is necessary for the selection of patients for treatment with crizotinib.[1]

Figure 1. Clinical pathway for patients with advanced NSCLC based on existing NICE clinical guidelines



Abbreviations: NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-L1, programmed-death ligand 1
Source: NICE clinical guidelines: lung cancer (NG122)[17]

B.1.4 Equality considerations

ROS1 rearrangement represents a very small population, with a reported prevalence of 1% to 2% among NSCLC patients. ROS1-positive NSCLC patients are disproportionately made up of young nonsmokers with non-squamous

adenocarcinomas. Targeted ROS1 inhibition offers the greatest clinical benefit for this patient group.

Since its availability through the CDF in 2018, crizotinib has become an established targeted treatment option for patients.[2] Real-world data on crizotinib use available from the Systemic Anti-Cancer Therapy (SACT) database demonstrates that despite the introduction of entrectinib, crizotinib remains a key choice for clinicians, with a consistent number of new patients treated with crizotinib each year (Section B.3.10.1)[20]. This data is further corroborated by market-share data.[21] Collectively, these data indicate the clinical need for crizotinib.

The European licence for crizotinib requires that an accurate and validated test for ROS1-positivity is performed for the selection of patients who would be able to receive treatment with crizotinib. Testing for ROS1-positivity, as described in the National Genomic Test Directory for Cancer since 2019/2020, is standard practice in England.[18]

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

As outlined in the decision problem, entrectinib is the sole comparator being considered in this analysis, given that it is the only other approved first-line therapy for ROS1-positive NSCLC. Relevant outcome measures identified in TA643 that were used to estimate the cost effectiveness of the comparator, entrectinib, included progression-free survival (PFS; the time from first dose of entrectinib to tumour progression or death due to any cause), overall survival (OS; time from first dose of entrectinib to death due to any cause), time on treatment (ToT), overall response rate (ORR; complete response and partial response), safety, and health-related quality-of-life (HRQoL).[19] The clinical outcomes and measures appraised in TA643 are presented in Table 3.

Table 3. Clinical outcomes and measures appraised in published NICE guidance for entrectinib (TA643)[19]

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
PFS	Months (median) Hazard ratio	Yes	Minor	A hazard ratio of 1 for the crizotinib to entrectinib comparison	Data were immature
OS	Months (median) Hazard ratio	Yes	Major	A hazard ratio of 1 for the crizotinib to entrectinib comparison	Data were immature and heavily censored, so only an interim analysis was available
ORR	Percentages	No	None	None	None
ToT	Months (median)	Yes	None	None	None
HRQoL	Utility scores	Yes	Medium	None	EQ-5D data were only available in the pre-progression state for the integrated entrectinib analysis and in the post-progression state for PROFILE 1014
Safety	Percentages	Yes	None	None	None

Abbreviations: AE: adverse event; ICER; incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; ToT: time on treatment

In TA643, no data were available for treatment of ROS1-positive NSCLC with pemetrexed plus platinum (the relevant comparator in the appraisal).[19] Therefore, the comparison of pemetrexed plus platinum to entrectinib was estimated using network meta-analysis (NMA) including a direct comparison of pemetrexed plus platinum to crizotinib.

Using one-way sensitivity analysis, their model demonstrated the key model driver with the greatest impact on the incremental cost-effectiveness ratio (ICER) values for the comparison of entrectinib with pemetrexed plus platinum and entrectinib with crizotinib was the OS hazard ratio (HR). Utility values had a moderate effect on the ICER and PFS HR values had limited influence on the ICER. Other outcomes considered in the model had inconsequential effects on the ICER.

OS and PFS for crizotinib were estimated from an unanchored matching adjusted indirect comparison (MAIC). Given the small population sizes and uncertainties in the data, the Evidence Review Group (ERG) considered estimated gains in OS and PFS by entrectinib relative to crizotinib implausible and assumed no differences between these outcomes from the two treatments (i.e., HR=1).

B.2.2 Resource use assumptions

Assumptions made in the submission for entrectinib (TA643) are summarised in Table 4.[19] The ERG's preferred assumption is indicated in cases where the original assumption was contested. Notably, ROS1 testing costs are no longer applicable since testing is routinely performed in England, as described in the National Genomic Test Directory for Cancer.[18]

Table 4. Resource use assumptions for TA643[19]

Assumption	Assumption description	ERG preferred assumption
Time horizon	30 years (lifetime horizon)	
Carboplatin target dose	AUC 5−6 mg/ml/min	
Max number of cycles of pemetrexed maintenance chemotherapy	A maximum number of 4 cycles Pemetrexed maintenance therapy only to patients who have received pemetrexed with cisplatin (therefore excluding patients who received pemetrexed with carboplatin)	• Pemetrexed continued until disease progression, up to 2 years. • Pemetrexed maintenance therapy to patients who have received pemetrexed with cisplatin or carboplatin
Cisplatin/carboplatin proportion in combination with pemetrexed chemotherapy	46% of patients receive carboplatin and 54% cisplatin	80% of patients receive carboplatin and 20% cisplatin
Resource use utilisation	Resource use utilisation is the same on all arms	
ROS1 testing	The costs of ROS1 testing is applied for the crizotinib and entrectinib arm.	

Company evidence submission: Crizotinib for treating ROS1-positive advanced non-small cell lung cancer.

Assumption	Assumption description	ERG preferred assumption
	Upfront testing approach is used in line with the accepted approach in TA529	
Entrectinib OS base case curve	Exponential	
Entrectinib PFS base case curve	Exponential	
Entrectinib ToT base case curve	Exponential	
Utility values in progression free	Utilities are the same for all treatment arms	
Pemetrexed plus platinum efficacy data source	The published HR from PROFILE 1014 was applied to the crizotinib arm.	
Comparator	Base case: Pemetrexed plus platinum As a key scenario: crizotinib	

Abbreviations: AUC, area under the curve; OS, overall survival; PFS, progression free survival; ROS1, ROS proto-oncogene 1; ToT, time on treatment
Source: NICE TA643, Table 59

The ERG disagreed with some of the company's assumptions on disease management resource use and provided their own which were made in consultation with experts to reflect contemporary UK clinical practice (Table 5).

Table 5. The ERG's preferred disease management resource use[19]

Resource required	Company assumptions				ERG preferred assumptions			
	Progression-free		Post-progression		Progression-free		Post-progression	
	% 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
Bio-chemistry	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

B.3 Clinical effectiveness

Clinical evidence base for crizotinib and entrectinib

- Currently, there is no randomised controlled trial (RCT) evidence available for crizotinib against its comparator, entrectinib.
- A *de novo* systematic literature review (SLR) of clinical evidence from RCTs, non-RCTs and single-arm studies was conducted to evaluate and present supporting evidence on the clinical similarity between crizotinib and entrectinib.

Systematic literature review

- The SLR identified eight studies reported in 18 publications assessing the efficacy, safety, tolerability, and quality of life (QoL) of crizotinib and entrectinib, from database inception to July 2023.
- This included one phase 1 study (PROFILE 1001), five phase 2 studies (OxOnc, METROS, EUCROSS, AcSé, STARTRK-2), one phase 2/3 study (B-FAST), and one pooled analysis comprising of phase 1/2 (ALKA-372-001, STARTRK-1) and phase 2 (STARTRK-2) studies.
- Five studies (PROFILE 1001, OxOnc, METROS, EUCROSS, AcSé) focused on crizotinib, while two studies (B-FAST, STARTRK-2) and one pooled analysis (ALKA-372-001, STARTRK-1, STARTRK-2) focused on the comparator, entrectinib.
- Similarity of crizotinib to entrectinib was generally observed. No clinically significant differences in safety and QoL were noted between treatment arms.
- Crizotinib and entrectinib exhibited substantially similar median overall survival (OS) and progression-free survival (PFS).
  - Median OS ranged from 17.2–51.4 months for crizotinib and 28.3–47.8 months for entrectinib.
  - Median PFS ranged from 5.5–22.8 months for crizotinib, and 12.5–15.7 months for entrectinib.
- Crizotinib showed an overall response rate (ORR) of at least 65%, while entrectinib demonstrated a similar ORR.
- Disease control rates (DCR) for crizotinib were between 71% and 90%, indicating comparable disease control to entrectinib (DCR of 67–84%).
- Duration of response (DOR) ranged from 19.7–24.7 months (except for EUCROSS, where results were not published) for crizotinib and 14.9–34.8 months for entrectinib.
- QoL data was limited, available for one crizotinib study (EUCROSS) and one entrectinib study (STARTRK-2), with non-significant results and no major impact reported.
- In terms of safety and tolerability, treatment-related adverse events were frequent (>90% incidence) for both crizotinib and entrectinib, with similar discontinuation rates of 2%-8.1% and 6.6%-21.7%, respectively, related to adverse events.
- Patients treated with crizotinib frequently experienced vision disorders and fatigue, while dysgeusia was commonly associated with entrectinib. Gastrointestinal issues occurred frequently with both crizotinib (vomiting, nausea, diarrhoea, constipation) and entrectinib (constipation, diarrhoea, nausea).

New data from PROFILE 1001 and Oxford Oncology (OxOnc) since the original TA529 submission in 2017

- **PROFILE 1001**: At 62.6 months median follow-up (Shaw *et al.* 2019), the median OS was 51.4 months, median PFS was 19.3 months, and median DOR was 24.7 months. Results were in line with the previous analysis (Shaw *et al.* 2014) at 16.4 months median follow-up. While AEs were seen in all patients in both analyses, grade 3 or 4 TRAEs reduced from 52.8% (2014) to 36% (2019).
- **OxOnc**: The updated analysis (Wu *et al.* 2022) reported a median OS of 44.2 months at 56.2 months median follow-up versus 32.5 months at 21.4 months median follow-up in the initial analysis (Wu *et al.* 2018). Median PFS and DOR were not reported in the updated analysis. TRAEs occurred in 97.6% patients, of which 32.3% were ≥ grade 3 TRAEs. Overall, the safety profile of crizotinib was consistent with PROFILE 1001.

Real world evidence (RWE)

- Based on data collected in the SACT database in England, patients treated with crizotinib for ROS1-positive NSCLC had a median OS of 21.9 months (95% CI, 17.7−29) at 60 months, which was lower than that seen in PROFILE 1001. Nonetheless, year-on-year SACT data (2018 to 2023) reflected a consistent increase in the number of patients receiving crizotinib, despite the introduction of entrectinib.
- RWE outcomes from published retrospective studies assessing crizotinib were similar to those seen in both crizotinib and entrectinib clinical studies, with the median OS ranging from 28.7–60 months, PFS from 9.1–23 months, and ORR from 62.5%–93.8%.
- Overall, the effectiveness outcomes from RWE were found to be consistent with clinical trial data and support the use of crizotinib in patients with ROS1-positive NSCLC. Efficacy between crizotinib and entrectinib was similar in ROS1-positive NSCLC, or at least no significant evidence was found to favour one treatment over the other.

Indirect treatment comparison

- A series of simulated treatment comparisons (STCs) were run for PFS, OS, DOR, and ORR between crizotinib and entrectinib:
  - For PFS, the HR of crizotinib versus entrectinib was reasonably constant, with a value of [redacted] Those findings suggest similar efficacy between crizotinib and entrectinib as the confidence intervals include 1, suggesting no significant differences in terms of PFS. For OS, the HR was [redacted] The results suggest similarity between crizotinib and entrectinib as HR estimates cross 1 over time and confidence intervals including 1, suggesting no significant differences in terms of OS.
  - For DOR, the HR started [redacted] Overall, DOR results suggest similarity between crizotinib and entrectinib as confidence intervals include 1.
  - For ORR, the OR of crizotinib vs entrectinib was [redacted]

- MAICs were run as sensitivity analyses to assess the uncertainty on PFS and OS results coming from the choice of distribution in the STC.
  - The base-case MAICs (adjusting on all covariates) resulted in a HR for PFS of crizotinib vs entrectinib of [redacted] for OS. The CIs contain 1 suggesting non-significant results and thus similar efficacy between crizotinib and entrectinib. However, since the assumptions of proportional hazard are not fully verified, the interpretation of this finding should be approached with caution and critical analysis.
  - The MAICs without ethnicity as adjustment covariate resulted in a HR of crizotinib vs entrectinib of [redacted] for PFS and [redacted]

B.3.1 Identification and selection of relevant studies

In the absence of head-to-head trials comparing crizotinib and entrectinib, a *de novo* SLR was carried out in July 2023 to identify relevant randomised controlled studies (RCTs), non-RCTs and single arm studies reporting on the efficacy, safety, tolerability, and quality of life (QoL) data for crizotinib and entrectinib in the treatment of ROS1-positive advanced NSCLC. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated. The identified studies were used to inform an indirect treatment comparison (ITC) presented in Section B.3.12.

B.3.2 List of relevant clinical effectiveness evidence

The SLR identified eight unique studies reported across 18 publications (11 full publications and seven conference abstracts).[22–39] All identified studies were single-arm trials, highlighting the lack of a common comparator between crizotinib and entrectinib studies. More information on the eight studies is presented in Table 6.

One study (PROFILE 1001) was a phase 1 study, five studies (OxOnc, METROS, EUCROSS, AcSé, STARTRK-2) were phase 2, one study was phase 2/3 (B-FAST), and one study was a pooled analysis comprising of phase 1/2 (ALKA-372-001, STARTRK-1) and phase 2 (STARTRK-2) studies. Five of the studies identified assessed crizotinib (PROFILE 1001, METROS, EUCROSS, AcSé and OxOnc) (ten publications) and two studies (B-FAST, STARTRK-2) complemented by one pooled analysis (ALKA-372-001, STARTRK-1, STARTRK-2) focused on entrectinib (eight publications). Study location varied, with Asia, Europe, and the USA being the most common regions.

Commonly assessed outcomes across the studies included the response rates (RR), PFS, OS, adverse events (AEs), and duration of response (DOR). Furthermore, commonly reported subgroups were the number of lines of therapies (LOTs), which varied for stratification, and central nervous system (CNS) metastases at baseline compared to no CNS metastases. Median follow-up ranged from 12–62.2 months for

patients receiving crizotinib and from 6–38.6 months in the entrectinib studies, with assessments typically performed every two months.

Table 6. Clinical effectiveness evidence

Study name and study number	Study design	Population	Intervention	Comparator	Indicate if study supports application for marketing authorisation	Reported outcomes specified in the decision problem	All other reported outcomes
PROFILE 1001 NCT00585195	Phase 1, open-label, multicentre study, carried out in Australia, South Korea, and the USA from 2006-2020	Patients with advanced NSCLC with a ROS1 rearrangement	Crizotinib 250 mg twice daily	N/A	Yes	• PFS • RR • OS • TTR • AEs • DOR • Treatment discontinuation	Mortality
OxOnc NCT01945021	Phase 2, open-label, multicentre study, carried out in China, Japan, South Korea, Taiwan from 2013-2016	East Asian patients with ROS1-positive advanced NSCLC who had received ≤3 LOT	Crizotinib 250 mg twice daily	N/A	Yes	• PFS • RR • OS • TTR • AEs • DOR • QoL • DCR	N/A
METROS NCT02499614	Phase 2, open-label, multicentre, non-comparative study, carried out in Italy from 2014-2017	Patients with locally advanced or metastatic NSCLC, pretreated with at least one previous chemotherapy line, with MET amplification, MET exon 14 mutation or ROS1 rearrangement	Crizotinib 250 mg BID until disease progression, unacceptable toxicity, or patient refusal.	N/A	No	• PFS • RR • OS • DOR • AEs • TTR	Depth of response
EUCROSS NCT02183870	Phase 2, open-label, multicentre study, carried out Germany, Spain and Switzerland from 2014-2020	Patients with locally advanced or metastatic NSCLC and ROS1 rearrangement	Crizotinib 250 mg twice daily	N/A	No	• PFS • RR • OS • DOR • AEs • DCR • QoL • Treatment interruption	Dose reduction
AcSé NCT02034981	Phase 2, open-label, single centre study, carried out in France	Patients with inoperable, historically confirmed locally advanced or metastatic NSCLC, for which no standard or curative	Crizotinib 250 mg BID continuously	N/A	No	• PFS • RR • OS • Treatment discontinuation	N/A

Study name and study number	Study design	Population	Intervention	Comparator	Indicate if study supports application for marketing authorisation	Reported outcomes specified in the decision problem	All other reported outcomes
		treatment was available; with *c-MET* ≥6 copies, *c-MET*-mutated, or *ROS1*-translocated tumours	over 28-day cycles.				
STARTRK-2 NCT02568267	Ongoing phase 2, open-label, multicentre study, carried out in Asia, Australia, Europe, USA	Patients with locally advanced or metastatic *NTRK1/2/3* and *ROS1* fusion-positive solid tumours	Entrectinib 600 mg once daily	N/A	No	• PFS • RR • OS • DOR • AEs • QoL	N/A
B-FAST NCT03178552	Ongoing phase 2/3, open-label, multicentre study, carried out in Asia, Central and South America, Europe, USA	Patients with treatment-naïve measurable stage 3B/4 NSCLC identified as ROS1-positive	Entrectinib 600 mg once daily	N/A	No	• PFS • RR • OS • DOR	N/A
Pooled analysis (ALKA-372-001 STARTRK-1 STARTRK-2) NCT02097810 NCT02568267	Partly ongoing phase 1/2, open-label, multicentre studies, carried out in Asia, Europe and USA	Patients with ROS1 fusion-positive NSCLC	Entrectinib 600 mg	N/A	No	• PFS • RR • OS • DOR • AEs • Treatment discontinuation	Treatment tolerance

Abbreviations: AEs: adverse events; BID: bis in die; DCR: disease control rate; DOR: duration of response; NSCLC: non-small cell lung cancer; LOT: lines of therapy; MET: mesenchymal epithelial transition; NTRK: neurotrophic tyrosine receptor kinase gene fusion; OS: overall survival; QoL: quality of life; PFS: progression-free survival; ROS1: proto-oncogene tyrosine-protein kinase 1; RR: response rate; TTR: time to tumour response; USA: United States of America

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Comparative summary of methodology for included studies

Four studies (PROFILE 1001, OxOnc, B-FAST, STARTRK-2) and the pooled analysis (ALKA-372-001, STARTRK-1 STARTRK-2) are international studies. METROS and AcSé are single-country studies, conducted in Italy and France respectively. EUCROSS was a European study conducted in Germany, Spain, and Switzerland. Most studies adopted a multicentre approach, with open-label, single-arm study design and were conducted as phase 1 and/ or phase 2 studies with B-FAST being the only phase 3 study. Patient eligibility criteria included histologically confirmed advanced or metastatic NSCLC, positive ROS1 gene translocations, and measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST). The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was commonly used to assess patient fitness for inclusion.

In terms of treatments, all crizotinib studies considered the monotherapy administered as 250 mg orally twice daily while entrectinib studies considered the 600 mg dose administered orally once per day. Concomitant medications were generally allowed for supportive care, while certain studies specified prohibited or permitted drugs to manage potential interactions.

Outcomes across studies focused on ORR, PFS, OS, safety and tolerability, DOR, and patient-reported outcomes. Subgroup analyses were conducted to explore variations based on factors such as age, ECOG status, gender, smoking status, and presence of brain metastases.

Table 7. Comparative summary of study methodology for crizotinib and entrectinib

Study name Data source(s)	Study design and setting	Study population	Intervention Comparator	Sample size	Outcomes assessed	Subgroup analyses	Timing of assessments
PROFILE 1001 **NCT00585195** **Primary:** Shaw, 2014[22] **Secondary:** Shaw, 2019[23]	Phase 1, open-label, multicentre **Location**: Australia, South Korea, USA **Study dates**: 2006–2020 **Molecular diagnosis**: FISH	Patients with advanced NSCLC with a ROS1 rearrangement	**Crizotinib** 250 mg twice daily, per oral administration	**Primary**: • Randomised / efficacy / safety analysis: 50 **Secondary**: • Efficacy / safety analysis: 53 (3 patients were retrospectively determined to be positive for ROS1 rearrangement)	• RR • TTR • DOR • PFS • OS • AEs • Treatment discontinuation	• Number of prior LOT (0 vs ≥1) • ECOG status (0 vs 1) • Age (<65 vs ≥65) • Male vs Female • Asian vs non-Asian	Every 2 months **Median follow-up**: • **Primary**: 16.4 months (data cut-off for safety data: April 2014; for efficacy data: May 2014) • **Secondary**: 62.6 months (data cut-off: June 2018)
OxOnc **NCT01945021** **Primary:** Wu, 2018[24] **Secondary:** Wu, 2022[25]	Phase 2, open-label, multicentre **Location**: China, Japan, South Korea, Taiwan **Study dates**: 2013–2016 **Molecular diagnosis**: AmoyDx RT-PCR or IHC or FISH	East Asian patients with ROS1-positive advanced NSCLC who had received ≤3 LOT	**Crizotinib** 250 mg twice daily	127 included in efficacy/safety analysis	• RR • PFS • OS • DOR • TTR* • DCR* • AEs • QoL	• CNS metastases at baseline vs no CNS metastases	Every 2 months for 8 cycles then every 3 months **Median follow-up** • Primary 21.4 months (data cut-off: July 2016) • Wu, 2022: 56.1 months (data cut-off: July 2020)

Study name Data source(s)	Study design and setting	Study population	Intervention Comparator	Sample size	Outcomes assessed	Subgroup analyses	Timing of assessments
METROS, NCT02499614 **Primary:** Landi, 2019[26] **Secondary:** Chiari, 2020[27] Cappuzzo, 2022[28]	Phase 2, open-label, multicentre, non-comparative study **Location**: Italy **Study dates**: 2014–2017 **Molecular diagnosis**: FISH	Patients with locally advanced or metastatic NSCLC, pre-treated with at least one previous chemotherapy line, with MET amplification, MET exon 14 mutation or ROS1 rearrangement	**Crizotinib** 250 mg BID until disease progression, unacceptable toxicity or patient refusal.	**Primary**: • Randomised: 33 • Efficacy analysis: 26 **Secondary**: • Chiari 2020: 48 (26 from primary analysis and 22 from expansion cohort) • Cappuzzo 2022: 64 (26 from primary analysis and 64 from expansion cohort)	• RR • PFS • OS • DOR • TTR • Depth of response • AEs	NR	• Tumour response by RECIST criteria • Toxicity graded according to the CTCAE version 4.0 **Median follow-up:** • Landi, 2019: 12 months (data cut-off: September 2017) • Chiari 2020: 36.4 months (data cut-off: NR) • Cappuzzo 2022: 54.4 months (data-cut-off: February 2022)
EUCROSS NCT02183870 **Primary:** Michels, 2019[29] **Secondary:** Michels, 2022[30]	Phase 2, open-label, multicentre **Location**: Germany, Spain, Switzerland **Study dates**: 2014–2020 **Molecular diagnosis**: FISH	Patients with locally advanced or metastatic NSCLC and ROS1 rearrangement	**Crizotinib** 250 mg twice daily	• Enrolled: 34 • Efficacy analysis: 30 • Safety analysis: 34	• RR • DCR • DOR* • TTR* • PFS • OS • AEs • Dose reduction	• Number of prior LOT: 0-1 vs ≥2 • CNS metastases at baseline vs no CNS metastases	• Every 6 weeks for 6 months, • Every 8 weeks for 6 months, • Every 12 weeks afterwards

Study name Data source(s)	Study design and setting	Study population	Intervention Comparator	Sample size	Outcomes assessed	Subgroup analyses	Timing of assessments
					• Treatment interruption • QoL		**Median follow-up**: • Michels, 2019; 20.6 months (data cut-off: April 2017) • Michels, 2022: 55.9 months (data cut-off: NR)
AcSé **NCT02034981** **Primary:** Moro-Sibilot, 2019[31]	Phase 2, open-label, single centre, **Location**: France **Study dates**: 2014–2023	Adults with advanced disease harbouring a genomic alteration in a crizotinib target (ALK, MET or ROS1). Patients could not be eligible for any other trial targeting the same genomic alteration.	**Crizotinib** 250 mg BID continuously over 28-day cycles.	78 screened with ROS1 translocated tumour, 37 included for efficacy/safety analysis	• RR • PFS • OS • Treatment discontinuation • DCR* • AEs*	NR	Every 2 months **Median follow-up**: NR
STARTRK-2 **NCT02568267** **Primary:** Paz-Ares, 2021[32] **Secondary:** Murakami, 2022[33]	Phase 2, open-label, multicentre **Location**: Asia, Australia, Europe, USA **Study dates**: 2015–2024	Patients with ROS1 fusion-positive NSCLC	**Entrectinib** 600 mg once daily	**Primary**: 145 in efficacy analysis 180 in safety analysis **Murakami, 2022**: 20 in efficacy analysis (Japanese)	• RR • DOR • TTR* • PFS • OS • AEs • QoL	• Japanese population • Chinese population • CNS metastases at baseline vs no CNS metastases	NR **Median follow-up**: • Primary: NR • Murakami, 2022: NR† (data cut-off: August 2021)

Study name Data source(s)	Study design and setting	Study population	Intervention Comparator	Sample size	Outcomes assessed	Subgroup analyses	Timing of assessments
Secondary: Lu, 2022[34]	**Molecular diagnosis**: NR			**Lu, 2022**: 38 in efficacy analysis (Chinese)			• Lu, 2022: ≥6 months (data cut-off: NR)
B-FAST NCT03178552 **Primary:** Peters, 2022[35]	Phase 2/3, open-label, multicentre **Location**: Asia, Central and South America, Europe, USA **Study dates**: 2017–2024 **Molecular diagnosis**: NR	Patients with treatment-naïve measurable stage 3B/4 NSCLC identified as ROS1-positive	**Entrectinib** 600 mg once daily	55 enrolled and treated, 54 in efficacy/safety analysis	• RR • DOR • PFS • TTR* • OS* • AEs* • QoL*	NR	Every 2 months **Median follow-up**: 18.3 months (data cut-off: November 2021)
ALKA-372-001, STARTRK-1 NCT02097810 , STARTRK-2 NCT02568267 **Pooled analysis:** Drilon, 2022[36] Dziadziuszko, 2021[37] Liu, 2020[38] Tan, 2020[39]	Phase 1/2, open-label, multicentre **Location**: Asia, Europe, USA **Study dates**: • ALKA-372-001: NR • STARTRK-1: 2014-2020 • STARTRK-2: 2015-2024 **Molecular diagnosis**: FoundationOne Liquid CDx	• Drillon 2022, Dziadziuszko 2021, Liu 2020: NSCLC ROS1 fusion-positive • Tan 2020 : Asian population NSCLC ROS1 fusion-positive	**Entrectinib** 600 mg	• Drillon, 2022: 168 in efficacy analysis, 224 in safety population • Dziadziuszko, 2021: 161 in efficacy analysis, 210 in safety analysis • Liu, 2020: 161 in efficacy analysis • Tan, 2020: 41 in efficacy analysis	• RR • DOR • PFS • OS • AEs • Treatment tolerance • Treatment discontinuation • TTR*	• CNS metastases at baseline vs no CNS metastases • 0 vs 1 vs 2 vs 3 prior LOT	After 4 weeks and then every 8 weeks Median follow-up: • Drilon, 2022: 29.1 months (data cut-off: May 2018) • Dziadziuszko, 2021: 15.8 months (data cut-off: May 2018) • Liu, 2020: NR (data cut-off: May 2019)

Study name Data source(s)	Study design and setting	Study population	Intervention Comparator	Sample size	Outcomes assessed	Subgroup analyses	Timing of assessments
							• Tan, 2020: 19.8 months (data cut-off: May 2019)

*Outcome reported in the trial protocol, but results are not published yet

†The follow-up period was described as >12 months in the abstract, but it was not reported in the poster.

Abbreviations: AE: adverse event; ALK: anaplastic lymphoma kinase; CGH: comparative genomic hybridisation; CNS: central nervous system; CTCAE: common terminology criteria for adverse events; DCR: disease control rate; DOR: duration of response; FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; LOT: line of therapy; MET: mesenchymal epithelial transition; NGS: next-generation sequencing; NR: not reported; NSCLC: non-small cell lung cancer NR: not reported; OS: overall survival; PFS: progression-free survival; pts: patients; ROS1: proto-oncogene tyrosine-protein kinase 1; RR: response rate; RT-PCR: reverse transcriptase polymerase chain reaction; TTF: time to treatment failure; TTR: time to tumour response; USA, United States of America

B.3.4 Study participant characteristics in included studies

The baseline characteristics of ROS1-positive NSCLC patients in the identified studies are presented in Table 8.

Median patient age ranged from 50−62 years for crizotinib, while patients treated with entrectinib had a median age range of 54−56 years. The proportion of males ranged from 30% to 43% in patients receiving crizotinib while for entrectinib, the range varied from 34.5% to 40%.[32,36] Ethnicity information was limited across crizotinib cohorts. While PROFILE 1001 presented a multi-ethnic cohort with 57% Caucasian, 40% Asian and 4% black patients, EUCROSS primarily included 91% Caucasian patients.[22,23,29] On the other hand, OxOnc was conducted exclusively in East Asian patients, including 58.3% Chinese, 20.5% Japanese, and 21.2% from other ethnic backgrounds.[24,25] A notable representation of Asian participants was also seen in the entrectinib studies ranging from 44.7%–100%.[32,39]

Patients treated with crizotinib were either untreated (13%−21%) or had received multiple prior LOTs, with the majority in the one prior LOT group (35%−76%). A similar trend was also seen in the studies evaluating entrectinib. AcSé was the only study that specified the type of treatments used prior to crizotinib: 97% of patients received chemotherapy, and 29% received an EGFR inhibitor.[31]

The ECOG PS scores had a similar distribution across studies evaluating crizotinib, with most patients scoring 1 (44%−73.2%) or 0 (26.8%−43%), and less than 5% patients in the METROS and AcSé studies scoring 2 or more. For entrectinib, STARTRK-2 reported the ECOG PS score range of 0 to 4 (0: 42.2%, 1: 46.7%, 2: 10%, 3: 0.6%, 4: 0.6%).

Amongst the included patients, those who had never smoked accounted for over 50% of the total population (56.25%−75% in crizotinib cohorts and 64.3%−75% across entrectinib cohorts). While the definition varied across studies, the proportion of current and former smokers ranged from 25%−43.75% in patients treated with crizotinib and 35.7% in a pooled entrectinib cohort.

Evidence on brain metastases at baseline was very limited across the studies, as it was either not published or not commonly assessed prior to treatment (as is the case with PROFILE 1001). Amongst the available data, it was seen in 18.1%−21% patients across three crizotinib cohorts, and in 41.5% patients who were part of a pooled subgroup analysis of Asian patients receiving entrectinib, although this isn't representative of the overall entrectinib cohort.

Table 8. Characteristics of participants in the studies across treatment groups

Study name Author Year	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
Studies with patients receiving crizotinib									
PROFILE 1001 Shaw, 2019[23]	Advanced NSCLC with a ROS1 rearrangement	53	55 (25-81) **N (%):** <65: 38 (72) ≥65: 15 (28)	23 (43)	• White: 30 (57) • Asian: 21 (40) • Black: 2 (4)	• 0 LOT: 7 (13) • 1 LOT: 22 (42) • 2 LOT: 12 (23) • ≥3 LOT: 12 (23)	• 0: 23 (43) • 1: 29 (55)	NR	• Never: 40 (75) • Former: 13 (25)
OxOnc Wu, 2018[24] **OxOnc Wu, 2022[25†]**	East Asian patients with ROS1-positive advanced NSCLC who had received ≤3 LOT	127	51.5 (22.8–79.7)	54 (42.5)	• Asian: 127 (100) • China: 74 (58.3) • Japan: 26 (20.5) • Other: 27 (21.2)	• 0 LOT: 24 (18.9) • 1 LOT: 53 (41.7) • 2 LOT: 31 (24.4) • 3 LOT: 19 (15)	• 0: 34 (26.8) • 1: 93 (73.2)	23 (18.1)	• No: 91 (71.7) • Yes: 36 (28.3)
METROS Landi, 2019[26]	ROS1-positive NSCLC	26	68 (28–86)	10 (38)	NR	• 1 LOT: 20 (76) • 2 LOT: 3 (12) • >2 LOT: 3 (12)	• 0: 18 (69) • 1: 7 (27) • 2: 1 (4)	6 (23)	• Never: 14 (54) • Past: 9 (35) • Current: 3 (11)
METROS Chiari, 2020[27] (including expansion cohort)[‡]	ROS1-positive NSCLC	48[‡]	50 (24–82)	17 (35.4)	NR	NR	• 0–1: 46 (95.8) • ≥2: 2 (4.2)	NR	• Never: 27 (56.25) • Current/former: 21 (43.75)
	Subgroup: Patients with development of VTE	20	NR **N (%):** <50: 7 (35) ≥50: 13 (65)	7 (35)	NR	NR	• 0–1: 18 (90) • ≥2: 2 (10)	NR	• Current/former: 10 (50.0) • Never: 10 (50.0)
	Subgroup: Patients with no development of VTE	28	NR **N (%):** <50: 15 (53.6) ≥50: 13 (46.4)	10 (35.7)	NR	NR	• 0–1: 28 (100) • ≥2: 0 (0)	NR	• Current/former: 11 (39.3) • Never: 17 (60.7)
EUCROSS Michels, 2019[29] Michels, 2022[30]	Locally advanced or metastatic NSCLC and ROS1 rearrangement	34	56 (33–84)	15 (44)	• Caucasian: 31 (91) • Asian: 2 (6) • Other: 1 (3)	• 0 LOT: 7 (21) • 1 LOT: 12 (35) • 2 LOT: 5 (15) • >2 LOT: 10 (29)	• 0: 12 (35) • 1: 20 (59) • 2: 2 (6)	7 (21)	• Never: 23 (68) • Ex-smoker: 11 (32)
AcSé Moro-Sibilot, 2019[31]	Inoperable, historically confirmed locally	37	62 (33–81)	11 (30)	NR	• Chemotherapy: 36 (97)	• 0: 11 (31) • 1: 16 (44) • 2: 9 (5)	8 (21)	• Smoking history: 11 (30)

Study name Author Year	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
	advanced or metastatic NSCLC with ROS1-translocation					• EGFR inhibitor: 11 (29) • Median number of LOT: 2 (1–7)	• Missing: 1		
Studies with patients receiving entrectinib									
STARTRK-2 Paz-Ares, 2021[32]	ROS1 fusion-positive NSCLC	**Safety**: 180	54 (15–86)	72 (40)	• Asian: 80 (44.7) • Black: 10 (5.6) • White: 76 (42.5) • Other/unknown: 3 (1.7) • NR: 10 (5.6)	NR	• 0: 76 (42.2) • 1: 84 (46.7) • 2: 18 (10) • 3: 1 (0.6) • 4: 1 (0.6)	NR	NR
		Efficacy: 145	54 (20–86)	52 (35.9)	• Asian: 68 (46.9) • Black: 7 (4.8) • White: 60 (41.4) • Other: 2 (1.4) • NR: 8 (5.5)	NR	• 0: 61 (42.1) • 1: 69 (47.6) • 2: 15 (10.3)	NR	NR
STARTRK-2 Murakami, 2022[33]	**Subgroup**: Japanese patients	20	51.0 (33–76)	NR	Japanese	• 0 LOT: 4 (20) • 1 LOT: 5 (25) • 2 LOT: 5 (25) • ≥3: 6 (30)	• 0: 11 (55) • 1: 8 (40) • 2: 1 (5)	NR	NR
STARTRK-2 Lu, 2022[34]	**Subgroup**: Chinese patients	38	NR	NR	Chinese	NR	NR	NR	NR
B-FAST Peters, 2022[35]	Treatment-naïve measurable stage 3B/4 NSCLC identified as ROS1-positive	55	56	42	NR	NR	NR	NR	• No history of tobacco use: (75)
ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[36]*	ROS1 fusion-positive, locally advanced, or metastatic NSCLC	168	54.0 (20–86)	58 (34.5)	• Asian: 78 (46.4) • White: 72 (42.9) • Black: 8 (4.8) • Other: 2 (1.2)	• CT: 115 (68.5) • Immunotherapy: 27 (16.1) • Targeted therapy: 14 (8.3) • Hormonal therapy: 1 (0.6) • RT: 27 (46.6)	• 0: 66 (39.3) • 1: 86 (51.2) • 2: 16 (9.5)	NR	• Never: 108 (64.3) • Previous or current: 60 (35.7)

Study name Author Year	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
ALKA-372-001, STARTRK-1, STARTRK-2 Dziadziuszko, 2021[37]*	Patients with ROS1 TKI naïve with locally advanced/ metastatic NSCLC	161	54.0 (20–86)	57 (35.4)	• Asian: 73 (45.3) • White: 71 (44.1) • Black: 7 (4.3) • Other: 2 (2.1) • NR: 8 (5)	• CT: 110 (68.3) • Immunotherapy: 21 (14.9) • Targeted therapy: 14 (8.7) • Hormonal therapy: 1 (0.6)	• 0: 60 (37.3) • 1: 64 (39.8) • ≥2: 37 (23)	NR	NR
ALKA-372-001, STARTRK-1, STARTRK-2 Tan, 2020[39]*	Asian patients with ROS1 TKI naïve with locally advanced /metastatic NSCLC	41	NR	NR	Asian: 41 (100)	NR	NR	17 (41.5)	NR
ALKA-372-001, STARTRK-1, STARTRK-2 Liu, 2020[38]*	Patients with locally advanced/ metastatic ROS1-positive NSCLC	161	NR	NR	NR	• 0 LOT: 31 (33) • 1 LOT: 38 (40.4) • 2 LOT: 13 (13.8) • ≥3 LOT: 12 (12.8)	NR	NR	NR

*****The clinical cut-off was 31 August 2020 in Drilon *et al*., 2022, and 1 May 2019, for Dziadziuszko *et al*., 2021, Tan *et al*., 2020, and Liu *et al*., 2020.
†Wu 2022 has the same patient characteristics as it followed up the same subjects from Wu 2018 for an additional 3 years.
‡ including 26 patients from the primary analysis and 22 patients from the expansion cohort
Abbreviations: CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; LOT, line of therapy; MET: mesenchymal epithelial transition; NSCLC: non-small cell lung cancer; NR, not reported; ROS1: proto-oncogene tyrosine-protein kinase; RT: radiotherapy; TKI: tyrosine kinase inhibitor; VTE: venous thromboembolism

B.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Seven of the eight identified studies were primary analyses, and one involved a pooled analysis of three studies (ALKA-372-001, STARTRK-1 NCT02097810, STARTRK-2). The definition of study groups and statistical analyses performed are displayed in Table 9.

The null hypothesis (H_0) in most studies posits a response rate of 10% or less, while alternative hypotheses (H_A) vary, suggesting response rates greater than 10%, 30%, and 40% (AcSé) or 50% (METROS and B-FAST). Most studies investigated the ORR as a primary endpoint. The STARTRK-2 study did not specify the primary endpoint but prespecified patient-reported outcomes (PROs) as secondary endpoints.

Included studies employed a range of statistical analyses, with Kaplan–Meier analysis being a recurrent choice for evaluating time-to-event data and using varying methods to calculate two-sided 95% confidence intervals such as the Brookmeyer–Crowley method (PROFILE 1001) or the exact method based on the F-distribution (OxOnc). Most studies also applied descriptive statistics to describe patient and disease characteristics.

While some studies explicitly detailed sample size considerations and power calculations (PROFILE 1001, OxOnc, METROS, EUCROSS) other studies provide limited information in this regard. Most studies which did further outline power calculations aimed to achieve at least 85% power to test H_0.

Most studies reported the number of patients completing and give various reasons for patients having stopped participation, for example due to AEs. None of the studies give further information regarding data management and handling of patient withdrawals.

Table 9. Summary of statistical analyses

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PROFILE 1001 (NCT00585195)	**Null hypothesis (H_0):** The rate of response to Crizotinib would be 10% or less. **Alternative hypothesis (H_A):** The rate of response rate to Crizotinib would be more than 10%. The primary endpoint was the overall response rate (ORR).	Kaplan–Meier analysis of time-to-event data to estimate median event times and the Brookmeyer–Crowley method to calculate two-sided 95% confidence intervals (CI). All analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute).	It was initially determined that 30 patients were needed to achieve a power of at least 85% to test the null hypothesis at a one-sided alpha level of 0.05 with the use of a single-stage design. For the alternative hypothesis, the response rate was assumed to be 30%. As of April 2012, there were eight responses (among 14 patients who could be evaluated), which exceeded the six responses required to reject the null hypothesis. To permit a more accurate assessment of the efficacy and safety of crizotinib in this population, we expanded the sample size to a maximum of 50 patients.	The overall response rate was similar for the first 30 patients who were enrolled (67%) and the additional 20 patients who were enrolled (80%). Patients completing: 49/50 (98%). No information about management of patient withdrawals.
OxOnc (NCT01945021)	Null hypothesis (H_0): NR Alternative hypothesis (H_A): NR The primary endpoint was ORR by independent radiology review.	The ORR (percentage of patients with a best overall response of a confirmed complete or confirmed partial response) and DCR (percentage of patients with a confirmed complete or confirmed partial response or stable disease) by IRR were evaluated in the response-evaluable population, and the 95% CIs were calculated using the exact method on the basis	The safety analysis population included all enrolled patients who received at least one dose of crizotinib; the response-evaluable population was defined as all patients in the safety analysis population who had an adequate baseline tumour assessment. An ORR of 30% was considered a clinically meaningful threshold for this	Patients completing: 126/127 (99%). At the data cutoff, median duration of crizotinib treatment was 18.4 months (range, 0.1–34.1 months), and 63 patients (49.6%) were still receiving crizotinib.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		of the F-distribution. DOR was summarised by Kaplan-Meier method and descriptive statistics; TTR was summarised using descriptive statistics only. DOR and TTR were assessed only in the subgroup of responder-patients in the response-evaluable population. In the safety analysis population, the Kaplan-Meier method was used to estimate median PFS and OS; two-sided 95% CIs are provided. PRO end points were analysed in the PRO-evaluable population (all patients in the safety analysis population who completed a baseline and one or more post–baseline PRO assessments). Changes in EORTC QLQ-C30 and QLQ-LC13 scores of ≥ 10 points from baseline were considered clinically meaningful and statistically significant if the 95% CIs did not include 0.	study, and a lower limit of the two-sided 95% CI around the observed ORR greater than this threshold would demonstrate the efficacy of crizotinib. By assuming a 50% true ORR, the statistical power to demonstrate efficacy on the basis of this threshold was 98.2% with 100 evaluable patients; the 95% CI for an observed ORR of 50% is 40% to 60%. A total of 110 patients were projected to be enrolled.	No information about management of patient withdrawals.
METROS (NCT02499614)	**Null hypothesis (H_0):** The rate of response to Crizotinib would be 10% or less.	Patients and disease characteristics were analysed using descriptive statistics and	Significance level of 5% (one sided) was assumed in each arm with a power of 98%.	Overall, TRAEs leading to dose reduction, temporary or permanent of discontinuation of

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	Alternative hypothesis (H_A): The rate of response rate to Crizotinib would be more than 50%. The primary endpoint was the ORR.	expressed as relative frequency (percentage) for discrete variables or median and interquartile range (IQR) for continuous variables. Associations among factors were evaluated with the x^2 test. Differences in distribution of quantitative variables were measured with the Mann–Whitney test. Confidence interval (95%) for ORR was calculated according to the exact method. PFS and OS were calculated from the date of starting therapy to the date of first evidence of either disease progression or death of the patient in the absence of documented disease progression (PFS), or death for any cause (OS). Patients without an event were censored at the date of last follow-up. Survival times were estimated using Kaplan–Meier analysis and expressed as medians with	The study was originally designed to include only MET-amplified NSCLCs. However, clinical data published in 2015 suggested MET exon 14-mutated NSCLCs as an additional population potentially benefiting to crizotinib. For such reason, the study was amended to include also patients with such aberration without modification in the statistical plan.	the drug were reported in 8 (15%), 13 (25%), and 3 (6%) patients. Among 13 serious AEs (SAE) reported, only two were judged as related to study drug. Patients completing: 48/52 (92%) No information about management of patient withdrawals.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		corresponding two-sided 95% CI. Differences between curves were evaluated using the log-rank test.		
B-FAST (NCT03178552)	**Null hypothesis (H_0):** The rate of response to Crizotinib would be 10% or less. **Alternative hypothesis (H_A):** The rate of response rate to Crizotinib would be more than 50%. The primary endpoint was the ORR.	Single-arm analysis, no other methods reported.	Not reported.	Adults (≥18 years) with treatment-naïve measurable stage 3B/4 NSCLC received oral entrectinib 600 mg day^{-1} until disease progression, unacceptable toxicity, consent withdrawal or death. Patients completing: NR No information about management of patient withdrawals.
EUCROSS (NCT02183870)	Null hypothesis (H_0): NR Alternative hypothesis (H_A): NR The primary endpoint was the ORR.	CIsm (level 95%) were calculated for all endpoint analyses if applicable. Time-to-event data (PFS, OS, and DOR) were summarised by the Kaplan-Meier estimator. Statistical significance for differences in time-to-event endpoints between different strata was calculated using the log rank test and for differences	For sample size calculation based on ORR according to Fleming's single-stage design, the following assumptions were prespecified: alpha 0.05, power 92%, lower proportion for rejection 20%, and a higher proportion for acceptance 45%, resulting in a sample size of 30 patients. The minimum number of objective responses to indicate effective treatment was 11 among the first 30 response-evaluable patients.	Patients completing: 19/35 (54%). No information about management of patient withdrawals.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		in proportions using Fisher's exact test.		
AcSé (NCT02034981)	In the NSCLC cohorts, c-MET ≥6 copies and c-MET-mutations: **Null hypothesis (H_0):** The rate of response to Crizotinib would be 10% or less. **Alternative hypothesis (H_A):** The rate of response rate to Crizotinib would be more than 30%. In the ROS-1 cohort, a higher success rate was expected, leading to different hypotheses: **Null hypothesis (H_0):** The rate of response to Crizotinib would be 20% or less. **Alternative hypothesis (H_A):** The rate of response rate to Crizotinib would be more than 40%. The primary endpoint was the ORR.	The AcSé crizotinib cohorts were designed with a two-stage Simon design. PFS, OS, DOR, clinical benefit rate, and duration of clinical benefit were analysed per cohort. Both survival times (PFS and OS) were analysed using the Kaplan–Meier method, with Rothman CIs. Safety (CTCAE v 4.0) was recorded as the worst grade per category per patient and per cycle. Safety data were presented per cycle and overall (worst grade for a given toxicity category over the whole treatment duration).	Patients were included in three cohorts according to their molecular profile: c-MET ≥6 copies, c-MET-mutations, and ROS-1 translocations. Overall, 5,606 NSCLC patients had tumour samples tested for c-MET number of copies (N=4,193), for c-MET-mutation (N=1,192), and for ROS-1 translocation (N=4,066).	Patients completing: NR. Patients were treated with oral crizotinib, 250 mg twice daily, until disease progression, patient withdrawal, or for any other reason in the interest of the patient. No information about management of patient withdrawals.
STARTRK-2 (NCT02568267)	Null hypothesis (H_0): NR Alternative hypothesis (H_A): NR The primary endpoint was not reported. Patient-reported outcomes (PROs) were	Analyses of QLQ-C30, QLQ-LC13, and QLQ-CR29 scores were conducted in the EA-PRO population to assess common tumour-related symptoms, functioning, and GHS/QoL.	The threshold for data evaluation was 25% of the SA-PRO or EA-PRO populations remaining enrolled and participating in the PRO questionnaires, in order to	Patients completed: NR. Reasons for discontinuation were death, consent withdrawal, loss to follow-up and other.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	prespecified as secondary endpoints.	Analyses of QLQ-C30 treatment-related symptoms were conducted in the SA-PRO population. PRO data were summarised with descriptive statistics. PROs were scored according to the developers' scoring manual. All scales and single-item measures were linearly transformed to a score range of 0–100. High scores on functional/GHS scales represent a high level of functioning and high HRQoL, respectively. Conversely, high symptom scores represent greater symptomatology severity.	optimise the generalisability of the results.	No information about management of patient withdrawals.
ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	**Null hypothesis (H_0): NR** **Alternative hypothesis (H_A): NR** The primary endpoints were ORR and DOR. Analysis of the post-crizotinib cohort was exploratory and used the same methods as the efficacy-assessable population.	For response data, the number, percentage, and corresponding two-sided 95% Clopper-Pearson exact CIs were summarised. The Kaplan-Meier method was used to estimate time-to-event end points with corresponding 95% CI. A competing risk analysis of CNS progression, with non-CNS progression and death as competing events, was carried out and cumulative incidence functions were estimated for each of these events.	Patients were enrolled in this cohort under a two-stage sequential testing design. Up to 13 patients were to be enrolled sequentially in the first stage; this stage would be deemed successful on the fourth responder, and enrolment would continue to the second stage, otherwise, enrolment would be stopped.	All the studies included in this analysis were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Patients received oral entrectinib 600 mg day^{-1} until documented radiographic disease progression, unacceptable toxicity, or withdrawal of consent.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		There was no formal hypothesis testing, and significance tests were not performed. Patient demographic and safety data were summarised descriptively.		

Abbreviations: CI: confidence interval; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; DCR: Disease control rate; DOR: Duration of response; EORTC: European Organisation for Research and Treatment of Cancer; IQR: interquartile range; NSCLC: Non-Small Cell Lung Cancer; MET: Mesenchymal epithelial transition; NR: not reported; ORR: overall response rate; OS: Overall survival; PFS: Progression-free survival; PRO: patient-reported outcomes; QLQ: quality of life questionnaire; TRAEs: Treatment-related adverse events; TTR: Time to tumour response

B.3.6 Critical appraisal of the relevant clinical effectiveness evidence

All studies included in this document were non-randomised, single-arm, open-label and multi- or single-centre studies. Quality assessment was conducted for six studies (PROFILE 1001, OxOnc, METROS, EUCROSS, AcSé, STARTRK-2) using the ROBINS-I tool.[40] This tool was chosen as it assesses the risk of bias in non-randomised studies of the effects of interventions (NRSI) and is frequently used in Cochrane reviews.[41] Two studies (B-FAST, and ALKA-372-001, STARTRK-1, STARTRK-2) were not assessed as one is a conference abstract and the other is a pooled analysis. Results of the quality assessment are presented in Table 10.

Overall, the findings suggest low risk of bias across all domains of the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) checklist for the included studies. Across all included studies, a low confounding bias was anticipated. Eligible patients were enrolled in the study simultaneously with the commencement of follow-up and intervention. There was no notable effect on assignment to or adherence to the intervention. Data completion was reasonably done with low measurement bias in outcome assessment, and there was no evidence of any additional outcomes than the ones reported.

Table 10. Quality assessment results

Study name	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall bias
PROFILE 1001 (NCT00585195)	Low	Low	Low	Low	Low	Low	Low	Low	Low
OxOnc (NCT01945021)	Low	Low	Low	Low	Low	Low	Low	Low	Low
METROS (NCT02499614)	Low	Low	Low	Low	Low	Low	Low	Low	Low
EUCROSS (NCT02183870)	Low	Low	Low	Low	Low	Low	Low	Low	Low
AcSé (NCT02034981)	Low	Low	Low	Low	Low	Low	Low	Low	Low
STARTRK-2 (NCT02568267)	Low	Low	Low	Low	Low	Low	Low	Low	Low

Definition of domains of the ROBINS-I[40]:
Q1: Confounding bias
Q2: Bias in selection of study participants
Q3: Risk of bias in classification of interventions
Q4: Deviations from intended interventions (effect of assignment to interventions)
Q5: Deviations from intended interventions (effect of adhering to interventions)
Q6: Missing outcome data
Q7: Measurement of the outcome
Q8: Bias in selection of reported result

B.3.7 Clinical effectiveness results of the relevant studies

Eight studies reporting on the efficacy, safety, and QoL outcomes associated with crizotinib (five studies) and entrectinib (three studies including one pooled analysis) were included in this submission. Overall, crizotinib and entrectinib exhibited similar median OS and PFS in the available studies. It should be noted that six studies reported immature OS data, indicating the need for longer follow up.[26,28–31,33–37] Crizotinib and entrectinib displayed comparable overall response and disease control rates (DCR). Furthermore, results from most of the included studies have shown that there were no clinically significant differences in the safety and QoL results between the treatment arms.

B.3.7.1 Overall survival

Median OS was reported for seven studies, and varied for crizotinib, ranging from 17.2 months (95% CI, 6.8–32.8) in AcSé to 51.4 months (95% CI, 29.3–not reached) in PROFILE 1001.[23,25,28–30,33,34,36,37,39] Only two studies reported mature OS data for crizotinib, PROFILE 1001 (51.4 months) and OxOnc (44.2 months).[23,25]

Two studies each for crizotinib and entrectinib (across six publications) assessed OS with landmark analyses.[26,29,30,33,36,37] The longest median duration of follow-up to assess the proportion of patients who received crizotinib with an OS event was 62.6 months in PROFILE 1001, compared to 38.6 months in patients received entrectinib in STARTRK-2.[23,33] In EUCROSS, the OS decreased from 82% (95% CI, 69–95) at 12 months to 60% (95% CI, 40–80) at 24 months in the intention-to-treat (ITT) population.[29] In the updated analysis, the proportion of patients with OS events for the response evaluable population were 65.6% (95% CI, 45.5–79.8) at 24 months, 58.7% (95% CI, 38.9–74) at 36 months, and 55% (95% CI, 35.4–70.9) at 48 months.[30]

In the pooled analysis (ALKA-372-001, STARTRK-1, and STARTRK-2) with entrectinib studies, Dziadziuszko *et al*., 2021 conducted landmark analyses at 6, 9, and 12 months, while Drilon *et al*., 2022, assessed OS at 12, 18, 24, and 36 months.[36,37] The two publications had different data cut-offs, hence the overlapping 12 months data has been retained.

B.3.7.2 Progression-free survival

Median PFS was reported in seven studies.[23,24,26,28,31,33–37,39] For crizotinib, the median PFS ranged from 5.5 months in AcSé to 22.8 months in METROS.[31,26] It should be noted that the population in AcSé consists of more heavily pre-treated patients compared to other trials.[31] In patients treated with entrectinib, PFS ranged from 12.5 months in B-FAST to 15.7 months in a pooled analysis (ALKA-372-001, STARTRK-1, STARTRK-2).[35–37] A subgroup of Japanese patients in STARTRK-2 reported a median PFS of 33.9 months.[33]

Table 11. Survival outcomes in patients with ROS1-positive NSCLC, as reported in clinical trials

Study name Data source(s)	Patient group	Median follow-up (months)	Intervention Comparator	Timepoint / Assessment	Number of patients	Overall survival		Progression-free survival	
						Median (95% CI)	% of patients with event (95%CI)	Median (95% CI)	% of patients with event (95%CI)
PROFILE 1001 Shaw, 2014[22*]	ROS1-positive NSCLC	16.4	Crizotinib	NR‖	50	NR	85 (72–93)	19.2 (11.4–not reached)	NR
PROFILE 1001 Shaw, 2019[23*]		62.6			53	51.4 (29.3–not reached)	NR	19.3 (15.2–39.1)	NR
OxOnc Wu 2018[24]	ROS1-positive NSCLC	21.4	Crizotinib	NR	127	32.5 (32.5–not reached)	NR	15.9 (12.9–24.0)	NR
OxOnc Wu 2022[25]		56.1				44.2 (32.0–not reached)	NR	NR	NR
METROS Landi 2019[26]	ROS1-positive NSCLC	12	Crizotinib	NR	26	NE	39	22.8 (15.2–30.3)	NR
				6 months	26	NR	96.2	NR	80.6
				12 months	26	NR	79.2	NR	71.9
METROS Cappuzzo 2022[28]	ROS1-positive NSCLC	54.4	Crizotinib	NR	64¥	40.5 (27.9–53.1)	NR	13.8 (7.4–20.2)	NR
AcSé Moro-Sibilot 2019[31]	ROS1-positive NSCLC	NR	Crizotinib	NR	37	17.2 (6.8–32.8)	NR	5.5 (4.2–9.1)	NR
EUCROSS Michels 2019[29]	ROS1-positive NSCLC**: ITT population**†	20.6	Crizotinib	NR	34	NE (20.3–NE)	68	NR	NR
				12 months	34	NR	82 (69–95)	NR	NR
				24 months	34	NR	60 (40–80)	NR	NR
EUCROSS Michels 2022[30]	ROS1-positive NSCLC: **response evaluable population**†	55.9	Crizotinib	24 months	30†	NR	65.6 (45.5–79.8)	NR	NR
				36 months	30†	NR	58.7 (38.9–74.0)	NR	NR
				48 months	30†	NR	55.0 (35.4–70.9)	NR	NR
STARTRK-2 Lu 2022[34]	ROS1-positive NSCLC – Chinese subgroup	≥6	Entrectinib	NR	38	40.2 (21.4–NE)	NR	17.7 (9.6–22.9)	NR
STARTRK-2	ROS1-positive NSCLC –	38.6	Entrectinib	NR	20	NE (15.7–NE)	NR	33.9 (10.4–40.1)	NR

Study name Data source(s)	Patient group	Median follow-up (months)	Intervention Comparator	Timepoint / Assessment	Number of patients	Overall survival		Progression-free survival	
						Median (95% CI)	% of patients with event (95%CI)	Median (95% CI)	% of patients with event (95%CI)
Murakami 2022[33]	Japanese subgroup			24 months	20	NR	65	NR	NR
B-FAST Peters 2022[35]	ROS1-positive NSCLC	18.3	Entrectinib	Investigator – assessed	NR	NR	NR	12.5 (8.7–18.5)	NR
				Dependent review facility – assessed	NR	NR	NR	14.8 (7.2–24.0)	NR
ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[36]	ROS1-positive NSCLC: efficacy evaluable population§	29.1	Entrectinib	NR	168	47.8 (44.1–NE)	32.1	15.7 (12.0–21.1)	NR
				12 months	168	NR	81 (75–88)	NR	57 (49–64)
				18 months	168	NR	74 (67–81)	NR	45 (37–53)
				24 months	168	NR	71 (63–78)	NR	40 (32–48)
				24 months	168	NR	71 (63–78)	NR	40 (32–48)
ALKA-372-001, STARTRK-1, STARTRK-2 Dziadziuszko, 2021[37]	ROS1-positive NSCLC : efficacy evaluable population§	15.8	Entrectinib	NR	161	NE (28.3–NE)	23.6	15.7 (11.0–21.1)	NR
				6 months	161	NR	91 (87–96)	NR	77 (70–84)
				9 months	161	NR	86 (81–92)	NR	66 (58–74)
				12 months	161	NR	81 (74–87)	NR	55 (47–64)
ALKA-372-001, STARTRK-1, STARTRK-2 Tan, 2020[39]	**Subgroup:** Asian patients with ROS1-positive NSCLC§	19.8	Entrectinib	NR	41	NE (28.3–NE)	NR	13.6 (7.7–NE)	NR

* Shaw *et al*., 2019 updated the data for the population at the data cut-off (30 June 2018), whereas the data cut-off date was 11 April 2014, in Shaw *et al*., 2014.
†Of the 34 patients who received at least one dose of crizotinib (ITT), 30 were included the primary efficacy analysis set.
¥ including 26 patients from the primary analysis and 38 patients from the expansion cohort
§The clinical cut-off was 31 August 2020, in Drilon *et al*., 2022, and 1 May 2019, for Dziadziuszko *et al*., 2021, and Tan *et al*., 2020.
Abbreviations: HR: hazard ratio; ITT: intention to treat; NE: not estimable; NR: Not reported, ROS1: Proto-oncogene tyrosine-protein kinase 1

B.3.7.3 Response rates

Overall response rates (also referred to as objective response rates) were reported in eight studies, including four studies conducted for each of crizotinib and entrectinib, as presented in Table 12. Generally, response rates achieved by the two treatments were similar.

For patients receiving crizotinib, the ORR across the four studies was 65%–72% in the response-evaluable populations, while complete response (CR) and partial response (PR) ranged between 0%–13.4% and 58.3%–70%, respectively.[23,24,26,29] Notably, the OxOnc study reported that the ORR with crizotinib treatment met the prospectively defined clinically meaningful threshold with the lower bound of the two-sided 95% CI >30%.[24] In this study, the ORR by independent radiology review was 71.7% (95% CI, 63.0–79.3) with 17 patients (13.4%) achieving CR and 74 patients (58.3%) achieving PR.

In pooled analyses of entrectinib studies (ALKA-372-001, STARTRK-1, STARTRK-2), the ORR for all trial participants was 67.1%–78%.[36,37,39]

The most striking difference in response rates reported by crizotinib and entrectinib was in the proportion of the populations achieving stable disease (SD). In the crizotinib-treated population, SD was observed in 16.5%–23.1% of patients.[23,24,26,29] Conversely, SD was achieved by 4.9%–8.9% of patients treated with entrectinib.[36,37,39]

B.3.7.3.1 Disease control rate

The overall DCR for patients treated with crizotinib ranged from 85% to 91%.[23,26] The overall DCR among patients who received entrectinib was comparable, varying from 76%–83% in the pooled analysis (ALKA-372-001, STARTRK-1, STARTRK-2).[37,39] A summary of the DCR across studies is presented in Table 13.

B.3.7.3.2 Duration of response

Most studies in which patients received crizotinib reported that responses were durable in the overall cohort. Patients experienced a relatively long-lasting response to crizotinib, with median DOR ranging between 19.7 (95% CI, 14.1–not reached)–24.7 (95% CI, 15.2–45.3) months (Table 12).[23] Clinical benefit was observed irrespective of the presence of brain metastases at baseline, number of prior lines of chemotherapy, enrolment country, age, sex, smoking status, or ECOG status.[24] In the pooled analysis (ALKA-372-001, STARTRK-1, STARTRK-2) evaluating entrectinib, the DOR ranged from 14.9 months (95% CI, 9.6–20.5) to 34.8 months (95% CI, 14.9–39.2).[36,37,39]

Table 12. Response rates in patients with ROS1-positive NSCLC

Study name Data source(s)	ROS1-positive NSCLC Patients / Subgroup	Intervention Comparator	Number of patients	Overall response rate %	CR %	PR %	DCR %	SD %	PD %	Median duration of response (95% CI)
PROFILE 1001 Shaw, 2014[22]	All patients	Crizotinib	50	72	3 (6)	66	90§	18*	6	17.6 (14.5–not reached)
PROFILE 1001 Shaw, 2019[23]			53	72	11	60	91§	19*	6	24.7 (15.2–45.3)
OxOnc Wu, 2018[24]‡	All patients	Crizotinib	127	71.7	13.4	58.3	88§	16.5	7.1	19.7 (14.1–not reached)
METROS Landi, 2019[26]	All patients	Crizotinib	26	65	4	61	85	23	4	21.4 (12.7–30.1)
EUCROSS Michels, 2019[29]	All patients – response-evaluable population‡	Crizotinib	30	70	0	70	90	20	6.7	NR
ALKA-372-001, STARTRK-1, STARTRK-2 Dziadziuszko, 2021[37]	All patients – efficacy evaluable population	Entrectinib	161	67.1	8.7	58.4	75.8§	8.7	9.3	15.7 (13.9–28.6)
ALKA-372-001, STARTRK-1, STARTRK-2 Tan, 2020[39]	All patients	Entrectinib	41	78	12.2	65.9	83§	4.9	7.3	14.9 (9.1–NE)
ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[36]	All patients – efficacy evaluable population	Entrectinib	168	67.9	13.1	54.8	76.8§	8.9	NR	20.5 (14.8–34.8)

*This data is reported after ≥6 weeks.
‡This data was assessed by local radiologic assessment. Value assessed by independent radiologists were also reported in the study.
§This data is calculated by adding PR, CR, and SD.
Abbreviations: CR: complete response; DCR: disease control rate; HR: hazard ratio, NR: not reported, NSCLC: non-small cell lung cancer, PD: progressive disease; PR: partial response; ROS1: proto-oncogene tyrosine-protein kinase 1; SD: standard deviation

B.3.7.3.3 Time to tumour response

Time to first response was reported in three studies evaluating crizotinib but was not reported for entrectinib.[22–24,26] It was defined as the date of the first dose of study drug to the date of the first documentation of PR or CR. Overall short times to tumour response (TTRs) were reported (Table 13). PROFILE 1001 reported a median time to first response at 7.9 weeks, though TTR ranged between 4.3–103.6 weeks.

Table 13. Time to tumour response

Study name Data source(s)	Patient group	Intervention	Number of patients	Median (range)	HR (95% CI); p-value
PROFILE 1001 **Shaw, 2019[23]***	ROS1-positive NSCLC	Crizotinib	53	7.9 weeks (4.3–103.6)	NR
OxOnc **Wu, 2018[24]**	ROS1-positive NSCLC	Crizotinib	127	1.9 months (1.6–15.8)	NR
METROS **Landi, 2019[26]**	ROS1-positive NSCLC	Crizotinib	26	7.9 weeks (IQR: 7.4–10.3)[t]	NR

*Shaw *et al*., 2019 updated the data for the population at the data cut-off (30 June 2018), whereas the data cut-off date was 11 April 2014, in Shaw *et al*., 2014.
[†]This data is reported as an interquartile range (IQR)
Abbreviations: HR: Hazard ratio; IQR: interquartile range; NR: not reported, NSCLC: non-small cell lung cancer, ROS1: proto-oncogene tyrosine-protein kinase 1.

B.3.7.3.4 Time-to-treatment failure

Time-to-treatment failure was only reported in the OxOnc study. Among the 63 patients who had disease progression during their crizotinib treatment, 68.3% (n=43) patients continued treatment for ≥3 weeks after progression (median duration, 20.7 weeks; range, 3.3–92.7).[24]

B.3.7.5 Quality of life outcomes

Only three studies reported QoL outcomes in patients receiving crizotinib (EUCROSS, OxOnc) and entrectinib (STARTRK-2) using the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ) C-30 and the lung specific EORTC QLQ LC-13.[25,29,32] A tabular summary of the mean scores is presented in Table 14.[29,32] OxOnc reported the improvement from baseline as a percentage, presented separately in Table 15.[25]

For the EORTC QLQ C-30, the score at baseline was similar in both EUCROSS and STARTRK-2 (58 and 56 respectively).[29,32] Patients receiving crizotinib in EUCROSS showed a progressive improvement in their QoL across cycles in EORTC QLQ C-30 mean score for the global health status/quality of life (GHS/QoL) domain (60±10 at cycle 1; 73.5±8 at cycle 18; 78.7±11 after cycle 24).[29] While study authors did not report a specific clinically meaningful threshold, an improvement of five to ten points has been considered clinically meaningful for lung cancer in previous publications.[32] OxOnc reported similar improvements for crizotinib from cycle 2.[25]

Patients receiving entrectinib in STARTRK-2 did not show any clinically meaningful improvement of GHS/QoL domains from baseline to cycle 18 (mean score of 56 and 60.1 respectively).[32] Functional scores in STARTRK-2 remained stable, but symptom severity decreased from baseline to cycle 18 for fatigue (change of mean score: −11.7), insomnia (change of mean score: −15), and appetite loss (change of mean score: −15.7), while constipation (change of mean score: −15) and diarrhoea (change of mean score: −15.7) severity increased.[32]

OxOnc reported the highest proportion of patients showing improvement, defined as ≥10-point decrease from cycle 2 to cycle 60: appetite loss (19%–33%), fatigue (23.0%–50.0%), dyspnoea (24.8%–41.3%), insomnia (24.6%–37.2%), and pain (33.6%–51.9%).[25] For functional domains, over half of the patients who received crizotinib experienced improvement or stable scores.

For the EORTC QLQ LC-13, a difference of ten points or more in the mean score is the threshold for clinical meaningfulness in EORTC QLQ LC-13 results. A higher score represents a higher severity of the evaluated symptom. For patients receiving crizotinib, there was a clinically meaningful decrease from baseline to cycle 18 in coughing severity (change in mean score: −23.5) and dyspnoea severity (change in mean score: −13.1).[29] From cycle 18 to cycle 24, the change of mean score for coughing and dyspnoea was not clinically significant. The authors stated bias may be introduced due to missing data, especially at later times. It is plausible that unfavourable score values tend to be preferentially missing at later times.[29]

In STARTRK-2, the mean score of EORTC QLQ LC-13 a clinical meaningful decrease in coughing severity was reported at cycle 18 for patients receiving entrectinib (change in mean score: −24.1).[32]

OxOnc reported the highest proportion of patients with improvement from cycle 2 to cycle 60 for symptoms, including coughing (42.6%–50.5%), pain in the chest (25.9%–35.3%), dyspnoea (22.1%–35.3%), and pain in the arm or shoulder (24.3%–35.3%).[25]

Table 14. Mean HRQoL scores in patients with ROS1-positive NSCLC

Study name Data source(s)	Patient group / Subgroup	Timepoint / Assessment	Number of patients	EORTC QLQ-C30 mean score (SD)	EORTC QLQ-LC13 mean score (SD)			
					Coughing	Dyspnoea	Haemoptysis	Chest pain
EUCROSS NCT02183870 Michels, 2019[29]	Patients with locally advanced or metastatic NSCLC and ROS1 rearrangement, receiving **crizotinib**	Baseline	QLQ-C30: 31 QLQ-LC13: 32	58 (10)	39.9 (11)	26.8 (8)	6.3 (7)	13.5 (7)
		Cycles 1–2	33	60 (10)	35 (8)	30 (8)	3.9 (4)	12.6 (7)
		Cycles 3–4	30	67.2 (6)	23.9 (8)	23.4 (8)	0.6 (1)	8.4 (6)
		Cycles 5–6	28	70 (7)	21.4 (10)	19 (7)	0.6 (1)	6.4 (6)
		Cycles 7–8	27	69.9 (8)	18.2(10)	20.5 (8)	0.7 (1)	5.2 (5)
		Cycles 9–10	27	69.5 (7)	18.8 (8)	21 (8)	0.08 (0)	4.2 (6)
		Cycles 11–12	25	71.2 (10)	22 (7)	22 (8)	0.05 (0)	8 (7)
		Cycles 13–14	23	73.1 (8)	15 (8)	17 (8)	1.2 (1)	5.7 (6)
		Cycles 15–16	21	73.4 (8	12.4 (8)	15.2 (8)	0.9 (1)	7 (7)
		Cycles 17–18	21	73.5 (8)	11.5 (8)	13.7 (7)	0.9 (1)	7 (7)
		Cycles 19–20	19	73.4 (9)	13.2(11)	15.9 (7)	1.9 (4)	5.3 (7)
		Cycles 21–22	15	73.2 (11)	16 (12)	17.3 (10)	0.3 (0)	6.6 (12)
		Cycles 23–24	10	75 (11)	14.3 (14)	14 (11)	3.5 (6)	6.8 (14)
		After 24th cycle	9	78.7 (11)	17.8 (12)	14.8 (12)	3.9 (7)	7.8 (14)
STARTRK-2 NCT02568267 Paz-Ares, 2021[32]*	Patients with ROS1 fusion-positive NSCLC, receiving **entrectinib**	Baseline	QLQ-C30: 142 QLQ-LC13: NR	56 (NR)	38.6 (NR)	32.3 (NR)	NR	18.6 (NR)
		Cycle 18	QLQ-C30: 37 QLQ-LC13: NR	4.1 (NR)	14.5 (NR)	26.1 (NR)	NR	14.9 (NR)

*Paz-Ares *et al*., 2021 reported the QLQ-C30 change from baseline to cycle 2–18 as a range value. Paz-Ares *et al*., 2021 also assessed HRQoL with EQ-5D-3L, but the results were not included in this publication.
Abbreviations: 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 lung-cancer quality of life questionnaire; NSCLC: non-small cell lung cancer; SD: standard deviation.

Table 15. Change in the proportion of patients with improvement from baseline in HRQoL

Study name Data source(s)	Patient group / Subgroup	Number of patients	Timepoint / assessment	Domain	*EORTC QLQ-C30*		*EORTC QLQ-LC13*	
					Improvement (% of patients)*	Stable scores (% of patients)	Improvement* *(% of patients)*	Stable scores (% of patients)
OxOnc NCT01945021 **Wu, 2022[25]**	Patients with ROS1-positive NSCLC, receiving crizotinib	127	Baseline	Physical	16.7	50.9	NA	NA
			Cycle 60		32.3	73.3	NA	NA
			Baseline	Role	13.8	45.5	NA	NA
			Cycle 60		33.3	66.7	NA	NA
			Baseline	Emotional	21.6	51.4	NA	NA
			Cycle 60		28.6	62.1	NA	NA
			Baseline	Cognitive	14	39.3	NA	NA
			Cycle 60		29.5	56.6	NA	NA
			Baseline	Social	21.6	41.8	NA	NA
			Cycle 60		31.6	67.5	NA	NA
			Cycle 2	Appetite loss	19	NR	NA	NA
			Cycle 60		33.3	NR	NA	NA
			Cycle 2	Fatigue	23	NR	NA	NA
			Cycle 60		50	NR	NA	NA
			Cycle 2	Dyspnoea	24.8	NR	NA	NA
			Cycle 60		41.3	NR	NA	NA
			Cycle 2	Insomnia	24.6	NR	NR	NR
			Cycle 60		37.2	NR	NR	NR
			Cycle 2	Pain	33.6	NR	NR	NR
			Cycle 60		51.9	NR	NR	NR
			Cycle 2	Coughing	NR	NR	42.6	NA
			Cycle 60		NR	NR	50.5	NA
			Cycle 2	Chest pain	NR	NR	25.9	NA
			Cycle 60		NR	NR	35.3	NA

*Improved status is defined as ≥10-point increase from baseline.
Abbreviations: 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 lung-cancer quality of life questionnaire; NSCLC: non-small cell lung cancer.

B.3.8 Subgroup analysis in PROFILE 1001

The pre-specified subgroup analysis required in PROFILE 1001 were reported in Table 7. The results of the subgroup analysis of ORR by baseline characteristics are presented in Appendix E. The point estimate of the ORR was provided along with the corresponding 95% CIs using the exact method based on the F-distribution.[23]

These analyses demonstrate the broad clinical effectiveness of crizotinib across various subgroups of patients with ROS1-positive advanced NSCLC. The subgroup analysis by number of prior therapies received showed that patients with no prior advanced/metastatic therapy (n=6) had an ORR of 85.7% (95% CI, 42.1–99.6), compared to patients who had received at least one prior advanced/metastatic therapy (n=31), where the ORR was 69.6% (95% CI, 54.2–82.3). However, due to the limited patient numbers, the ORR data by line of treatment is associated with high uncertainty.

It was also not possible to evaluate ORR for those with and without CNS metastases, due to the limitation of brain metastases at baseline not being commonly assessed prior to crizotinib initiation in PROFILE 1001. However, other clinical trials identified in the SLR reported ORR and other clinical outcomes for patients with and without CNS metastases at baseline, and have been summarised in Appendix E.

While these studies show that response rates for crizotinib and entrectinib remained stable in different subgroups, more comprehensive evidence on subgroups remains limited. Additionally, subgroup analysis was not conducted in the cost-comparison analysis presented in Section B.4.

B.3.9 New data from PROFILE 1001 and Oxford Oncology

Since the original crizotinib TA529 submission in 2017, there has been newly published data on OS and PFS as well as safety and tolerability from the two pivotal crizotinib phase 1 and 2 studies, PROFILE 1001 and Oxford Oncology (OxOnc).[2]

B.3.9.1 New data from PROFILE 1001

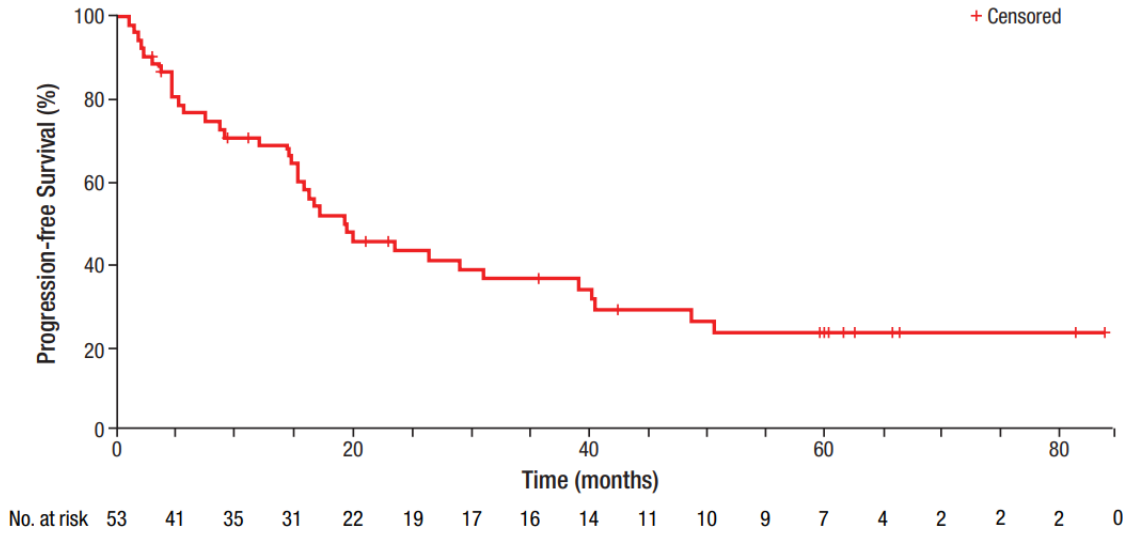
The first analysis for OS and PFS was performed for the PROFILE 1001 study in Shaw *et al*. in 2014, based on a data cut-off on 11 April 2014.[22] Median follow-up for OS was 16.4 months (95% CI, 13.8–19.8). Nine of 50 patients (18%) had died at data cut-off and OS at 12 months was 85% (95% CI, 72–93). Median PFS was 19.2 months (95% CI, 14.4–NR).[22]

In the updated analysis of PROFILE 1001 in Shaw *et al*., 2019, the median follow-up for OS was much longer at 62.6 months with a median OS of 51.4 months observed (95%CI, 29.3–NR). The median PFS was 19.3 months (95% CI, 15.2–39.1).[23] While the new data is consistent and in line with the previous analysis, the improvement in

OS is further demonstrated with clear and lasting separation of the Kaplan-Meier curves as shown in Figure 2 and Figure 3.

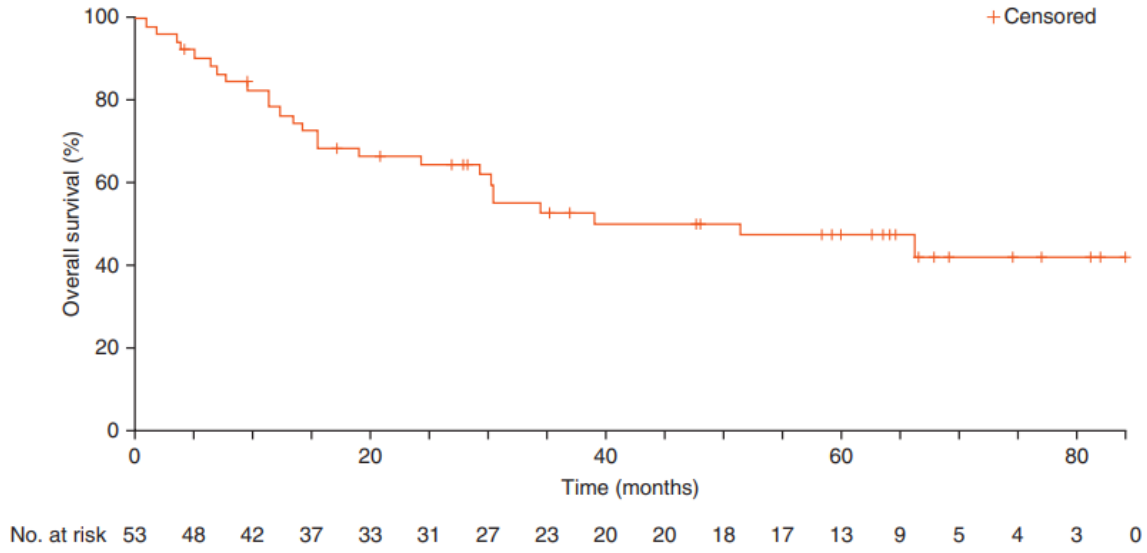
Furthermore, the DOR was longer in the updated analysis with a median DOR 24.7 months (95% CI, 15.2–45.3)[23] compared with 17.6 months (95% CI, 14.5–NR) in the initial study.[22]

Figure 2. Updated PFS Kaplan-Meier curves from PROFILE 1001



Source: Figure S2 in Shaw *et al.,* 2019[23]

Figure 3. Updated OS Kaplan-Meier curves from PROFILE 1001



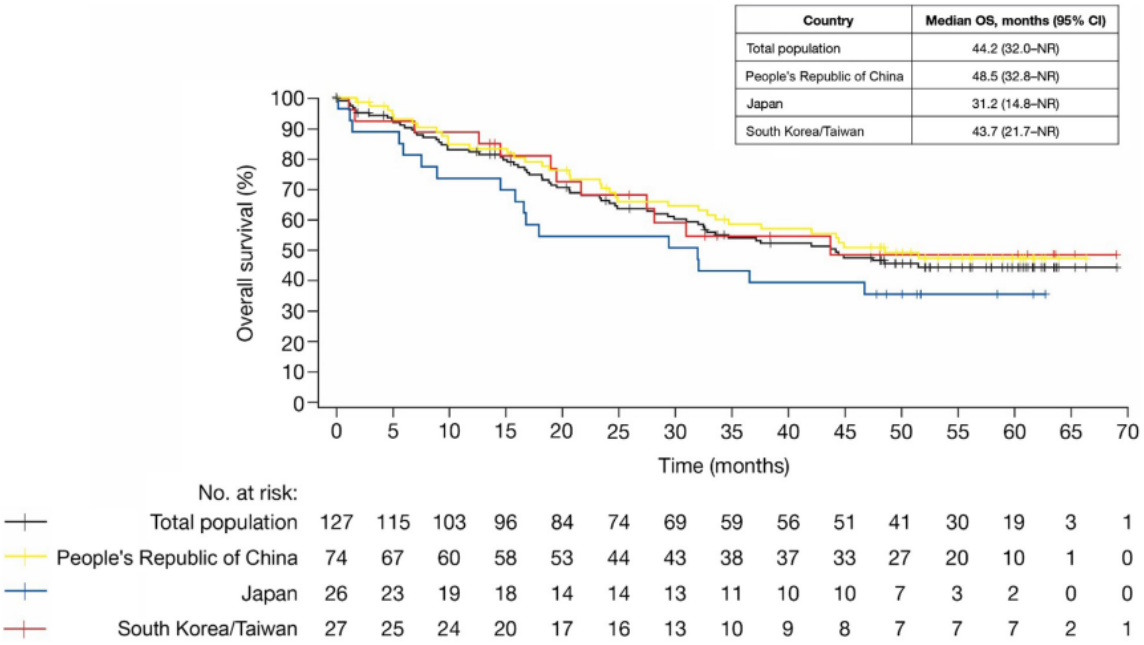
Source: page 1968, in Shaw *et al* 2019[23]

Additional improvements in patient response were seen regarding tolerability and safety outcomes. While AEs were seen in all patients in both analyses, grade 3 or 4 treatment-related AEs (TRAE) were seen in 52.8% (28 patients) in the initial analysis while this reduced to 36% (19 patients) in the updated analysis.[22,23] While one patient (2%) discontinued treatment due to TRAEs,[22] this was not the case for any patients in the updated analysis.[23]

B.3.9.2 New data from Oxford Oncology

Updated analysis from the OxOnc study is also in line with the previous observations from PROFILE 1001. In the first publication from 2018, the median duration of follow-up for OS was 21.4 months with median OS of 32.5 months (95% CI, 32.5–NR).[24] The updated analysis from 2022 showed an increased median OS of 44.2 months (95% CI, 32–NR) in the total population at a median follow-up of 56.2 months and is thus similar to the median OS observed in the updated PROFILE 1001 analysis.[23,25]

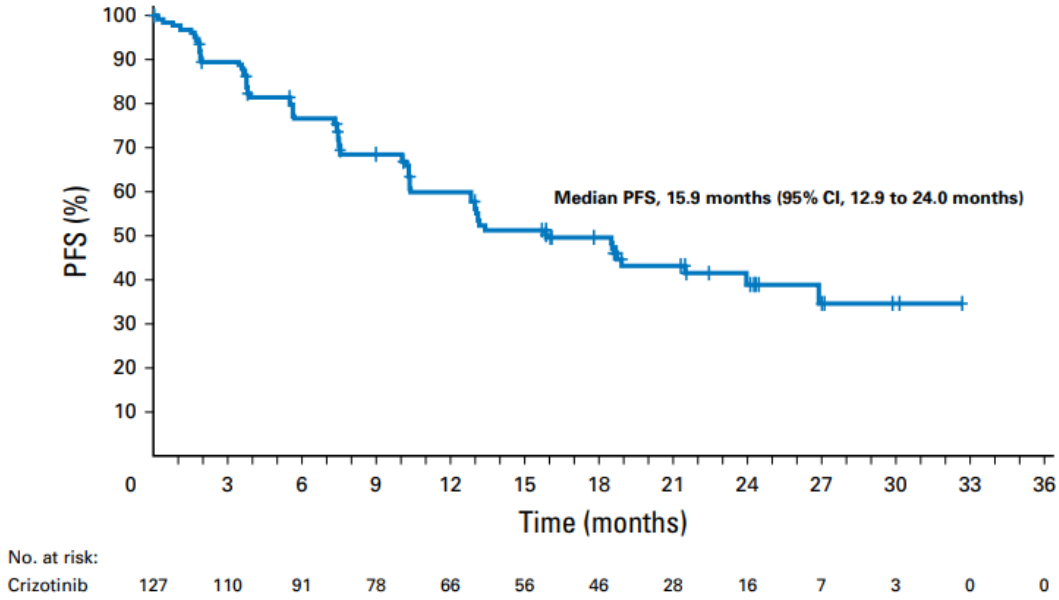
Figure 4. OS Kaplan-Meier curves from OxOnc



Source: page 5, in Wu *et al.,* 2022[25]

The median PFS in Wu *et al*., 2018 was reported as 15.9 months (95% CI, 12.9–24).[24] Wu *et al*., 2022 did not report median PFS. The median DOR in line with PROFILE 1001 analyses, at 19.7 months (95% CI,14.1–NR) in Wu *et al*., 2018, while DOR was not reported in Wu *et al*., 2022.[24,25]

Figure 5. PFS Kaplan-Meier curves from OxOnc



Source: page 1409, in Wu *et al.,* 2018[24]

The safety profile of crizotinib in OxOnc is consistent with PROFILE 1001. In the 2018 analysis, most TRAEs were grade 1 or 2 and occurred in 96.1% (122 patients). Grade 3 or 4 TRAEs were observed in 25.2% (32 patients). One patient permanently discontinued crizotinib due to grade 1 TRAEs (diarrhoea).[24] In the updated analysis, TRAEs occurred in 97.6 % (124 patients) of which 32.3% (40 patients) had grade 3 or 4 TRAEs. 2.4% (3 patients) discontinued the treatment due to TRAEs.[25]

B.3.10 Real-world evidence in crizotinib

B.3.10.1 Data from the Systemic Anti-Cancer Therapy (SACT) database

Real-world outcomes for patients in England receiving crizotinib in clinical practice for NSCLC during the CDF managed access period were collected in the SACT database and reported by the NHS National Disease Registration Service (NDRS).[20] The records of 163 unique patients with previously treated ROS1-positive advanced NSCLC, who applied for crizotinib treatment during the CDF period and had received at least one crizotinib dose, were analysed.[20]

In the SACT dataset (n=163), the median age was 63 years, 62 (38%) of the patients were male, and 58 (36%) of the patients had previously received more than one line of treatment (Table 16). The median treatment duration was 11.7 months, with a median follow-up of 17.4 months. The median OS was 21.9 (95% CI, 17.7–29) months (Table 17).[20] OS at 6 months was 82% (95% CI, 75–85), at 24 months was 46% (95% CI, 38–54), and at 60 months was 23% (95% CI, 14–33). Compared with the median OS observed in PROFILE 1001 (51.4 [95% CI, 29.3–not reached] months), the median

OS from the SACT data was comparatively shorter. It's worth noting that fewer patients had previously received more than one line of treatment (n=47, 87%) in PROFILE 1001, and the median follow-up period in PROFILE 1001 is much longer than in the SACT data. Additionally, the median age and percentage of males were similar between the SACT data and PROFILE 1001.

At the time of the latest data cut-off (30 June 2023), 126 (77%) of the 163 patients had concluded treatment.[20] A total of 54 (43%) had ended treatment due to disease progression, 28 (22%) due to death not during treatment, 17 (13%) due to death during treatment, and 12 (10%) due to acute toxicity.

Based on the year-on-year SACT data collection up to 60 months (May 2018 to June 2023), the number of patients receiving crizotinib consistently increased by more than 20 patients per year, from 113 at 36 months, to 136 at 48 months, and 163 patients at 60 months.[20,42,43] This demonstrates the sustained utilisation of crizotinib despite the introduction of entrectinib.

B.3.10.2 Peer-reviewed real-world evidence

Real-world evidence (RWE) for crizotinib is also available from 16 published retrospective studies, 10 of which were evaluated in a meta-analysis.[44] Patient characteristics for each of these studies are summarised in Table 17. Sample sizes ranged from 8–168 patients. The RWE studies were conducted in the USA, China, India, Italy, Japan, and Europe, similar to the distribution seen in the clinical trials. The median age across cohorts ranged from 50 to 68 years, and in instances where gender was reported, all but two patient populations were predominantly female. Other frequently reported patient characteristics include number of previous treatments, ECOG status, presence of brain metastases, and smoking history.

Median follow-up for RWE studies in the six studies in which mOS was reached was 15.3–35.5 months (Table 17). This exhibits less variability compared to the median follow-up from clinical trials, where mOS ranges between 28.7–60 months. Notably, the greatest median OS values were observed in trials in which crizotinib was administered in the first line. Median PFS was reported in 12 studies and ranged from 9.1–23 months. Across 14 studies, the ORR ranged from 62.5%–93.8% (Table 17). These outcomes demonstrated a similar trend when compared with the outcomes from the clinical trials evaluating crizotinib as well as entrectinib. Furthermore, patients without baseline CNS metastasis also achieved better PFS compared to those with baseline CNS metastases as like clinical trials.

A simulated treatment comparison (STC) was performed to compare clinical, outcomes from PROFILE 1001 to real-world outcomes from Waterhouse *et al*., 2022.[45] Median PFS and OS was greater in the clinical data compared to the real-world data. However, the differences were not significant, and the authors noted strong

imbalances in sex, age, ECOG PS, and smoking status between the two studies, which likely contributed to the differences in survival outcome measures.

AEs associated with crizotinib use for NSCLC with ROS1 gene fusions or MET alterations were reported as pooled-proportions across all included studies in the meta-analysis by Voung *et al.*, 2020.[44] AEs of any grade affecting at least one-third of patients included oedema (42.9%), vision impairment (43.7%), nausea (39.7%), vomiting (36.2%), diarrhoea (36.9%), fatigue (40.1%), and elevated transaminase (35.0%). The only AE of grade 3 or higher affecting at least 5% of trial participants was neutropenia (5.7%). Frequent AEs such as gastrointestinal issues and vision disorders were similarly observed in the clinical trials.

Waterhouse *et al*., 2022. reported the time to treatment discontinuation (TTD) and time to next treatment (TTNT) outcomes, which were not reported in the clinical trials.[45] Median TTD was 25.2 months (95% CI, 5.2−not reached) and restricted mean survival time for TTD at 42 months of follow-up was 21.9 months (95% CI, 15.7−28). For TTNT, ten patients (26.3%) received systemic anticancer therapy after crizotinib treatment.

B.3.10.3 RWE summary

Overall, the effectiveness outcomes from RWE were found to be consistent with clinical trial data and support the use of crizotinib in patients with ROS1-positive NSCLC. Efficacy between crizotinib and entrectinib was similar in ROS1-positive NSCLC, or at least no significant evidence was found to favour one treatment over the other. Furthermore, the SACT database assessment demonstrates the sustained utilisation of crizotinib as a treatment option despite the introduction of entrectinib. This trend is also supported by market share data from the Ipsos Oncology Monitor (2024), which reports the utilisation of first-line drugs for patients with ROS-1 positive NSCLC, excluding trials.[21] Crizotinib usage persisted even after the introduction of entrectinib, indicating a consistent number of new patients being initiated on crizotinib. Therefore, clinical and RWE support the maintenance of crizotinib's position alongside entrectinib in the current ROS1-positive NSCLC treatment guidelines (Figure 1).

Table 16. Patient characteristics at baseline in the RWE studies

Study name Author Year	Study design and setting	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
SACT database May 2018 to June 2023[20]*	Retrospective UK	ROS1-positive advanced NSCLC	163	63 • <40: 11 (7) • 40–49: 19 (12) • 50–59: 34 (21) • 60–69: 42 (26) • 70–79: 47 (29) 80+: 10 (6)	62 (38)	NR	Multiple prior therapies: 58 (36)	NR	NR	NR
Waterhouse, 2022[46]	Retrospective US	ROS1-positive advanced NSCLC	38	68 (IQR: 60–73)	13 (34.2)	• White: 27 (71.1) • Non-white: 11 (28.9)	Anticancer treatment: 13 (34.2)	• 0: 6 (15.8) • 1: 17 (44.7) • 2: 7 (18.4)	• Yes: 25 (65.8) • No: 13 (34.2)	• Current/former: 19 (55.9) • Never: 15 (44.1)
Zhang, 2021[47]	Retrospective China	ROS1-rearranged advanced NSCLC	168	52 (27–79)	105 (62)	NR	Radiation therapy: 14 (8.3)	• 0-1: 162 (96) • ≥ 2: 6 (4)	• Yes: 45 (27) • No: 123 (73)	• Current/former: 32 (19) • Non-smoker: 136 (81)
Xu, 2020[48]	Retrospective China	ROS1-positive advanced NSCLC	56	• ≥60: 19 (33.9) • <60: 37 (66.1)	15 (26.8)	NR	NR	• 0-1: 50 (89.3) • 2: 6 (10.7)	• Yes: 11 (19.6) • No: 45 (80.4)	Smoking history • No: 48 (85.7) • Yes: 8 (14.3)
Zheng, 2020[49]	Retrospective China	ROS1-rearranged advanced NSCLC	56	53 (24–72) • ≤65: 44 (78.6) • >60: 12 (21.4)	25 (44.6)	NR	NR	• 0: 12 (21.4) • 1 or 2: 44 (78.6)	11 (19.6)	• Never: 37 (66.1) • Smoker: 19 (33.9)
Capizzi 2019[50]†	Retrospective Italy	ROS1-positive advanced NSCLC	8	56.5‡ (46–67)	5 (62.5)	NR	• 1 LOT: 1 (12.5) • 2 LOT: 7 (87.5)	NR	0	• Never: 5 (62.5) • Light former: 2 (25) • Current: 1 (12.5)
Joshi 2019[51]†	Retrospective India	ROS1-positive advanced NSCLC	16 of 22‖	NA	NA	NA	• 1 LOT: 2 (12.5)	NA	NA	NA
Li, 2018[52]†	Retrospective China	ROS1-positive advanced NSCLC	36	50.8 (32–78)	18 (50)	NR	• 1 LOT: 14 (38.9) • 2 LOT: 15 (41.7)	• 0-1: 34 (94.4) • 2: 2 (5.6)	• Yes: 6 (16.7) • No: 30 (83.3)	Smoking status • No: 31 (86.1) • Yes: 5 (13.9)

Study name Author Year	Study design and setting	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
							• ≥3 LOT: 7 (19.4)			
Liu, 2019[53]†	Retrospective China	ROS1-rearranged advanced NSCLC	35	51 (26–82) • ≥65: 31 (88.6) • <65: 4 (11.4)	12 (34.3)	NR	• 1 LOT: 17 (48.6) • 2 LOT: 11 (31.4) • ≥3 LOT: 7 (20)	• 0: 1 (2.8) • 1: 31 (88.6) • 2: 3 (8.6)	8 (22.9)	NR
Masuda, 2019[54]†	Retrospective Japan	ROS1-rearranged advanced NSCLC	13	56 (36–78)	5 (38.5)	NR	• 1 LOT: 2 (15.4) • 2 LOT: 3 (23.1)	• 0: 5 (38.5) • 1: 6 (46.2) • 2: 2 (15.4)	4 (30.8)	Smoking history • No: 8 (61.5) • Yes: 5 (38.5)
Mazières, 2015[55]†	Retrospective Multi-Europe§	ROS1-rearrangement advanced NSCLC	31	50.5	11 (35.5)	NR	• 1 LOT: 1 (3.3) • 2 LOT: 9 (29) • 3 LOT: 5 (16.1) • ≥3 LOT: 16 (51.6)	NR	1 (3.2)	• Never: 22 (71) • Former: 6 (19.3) • Current: 3 (9.7)
Mehta 2020[56]†	Retrospective India	ROS1-positive advanced NSCLC	14 of 20‖	NR	NR	NR	• 1 LOT: 5 (35.7) • 2 LOT: 9 (64.3)	NR	NR	NR
Zeng, 2018[57]†	Retrospective China	ROS1-rearranged advanced NSCLC	19 of 22‖	NR	NR	NR	• 1 LOT: 14 (73.7) • 2 LOT: 2 (10.5) • ≥3 LOT: 3 (15.8)	NR	5 (26.3)	NR
Zhang, 2016[58]†	Retrospective China	ROS1-positive advanced NSCLC	15 of 51‖	NR	NR	NR	• ≥2 LOT: 15 (100)	NR	NR	NR
Zhu, 2019[59]†	Retrospective China	ROS1-positive advanced NSCLC	23	64 (35–79)	8 (34.8)	NR	• 1 LOT: 4 (17.4) • 2 LOT: 5 (21.7) • ≥3 LOT: 14 (60.9)	NR	NR	Smoking history • Yes: 2 (8.7) • No: 21 (91.3)

Study name Author Year	Study design and setting	Patient group	Number of patients	Age (years) Median (range)	Male n (%)	Ethnicity n (%)	Prior treatments n (%)	ECOG performance status n (%)	Brain metastases n (%)	Smoking status n (%)
Gainor, 2017[60]	Retrospective US	ROS1-positive advanced NSCLC	30 of 39‖	NR	NR	NR	• Platinum-doublet CT: 28 (93) • 2 LOT: 18 (60)	NR	NR	NR
Shen, 2020[61]	Retrospective China	ROS1-positive advanced NSCLC	30	51.5 (29–78) • ≤65: 22 (73.3) • >65: 8 (26.7)	9 (30)	NR	• 1 LOT: 30 (100)	NR	• Yes: 9 (30) • No: 21 (70)	• Never: 25 (83.3) • Ever/current:5 (16.7)

*This dataset, extracted from the National Disease Registration Service (NDRS), includes a snapshot of SACT data taken on 7 October 2023, encompassing SACT activity up until 30 June 2023.
†This study was extracted from the Vuong *et al*., 2020[44] systematic review and meta-analysis.
‡Mean data.
§Six European countries are France, Switzerland, Italy, Germany, Poland, and the Netherlands.
‖In these studies, only a subset of patients received crizotinib treatment among ROS1-positive patients.
Abbreviations: CT: chemotherapy; MET: mesenchymal epithelial transition factor receptor; NSCLC: non-small cell lung cancer; NA: Not applicable; NR: Not reported, ROS1: proto-oncogene tyrosine-protein kinase 1; SACT: Systemic Anti-Cancer Therapy; US: United States

Table 17. Clinical outcomes in patients with ROS1-positive NSCLC, as reported in the RWE studies

Study name Data source(s)	Line of therapy	Median follow-up (Months)	Timepoint / Assessment	Number of patients	Median (95% CI)		% of patients with event (95% CI)		ORR %	CR %	PR %	DCR %	SD %	PD %
					OS	PFS	OS	PFS						
SACT database May 2018 to June 2023[20]	Mixed	17.4	6 months	NR	NR	NR	82 (75–87)	NR	NR	NR	NR	NR	NR	NR
			12 months	NR	NR	NR	68 (61–75)	NR	NR	NR	NR	NR	NR	NR
			18 months	NR	NR	NR	58 (50–65)	NR	NR	NR	NR	NR	NR	NR
			24 months	NR	NR	NR	46 (38–54)	NR	NR	NR	NR	NR	NR	NR
		15.6	36 months	113	21.7	NR	34 (26–42)	NR	NR	NR	NR	NR	NR	NR
		17.2	48 months	136	21.9 (17.1–29.4)	NR	26 (18–35)	NR	NR	NR	NR	NR	NR	NR
		17.4	60 months	163	21.9 (17.7–29)	NR	23 (14–33)	NR	NR	NR	NR	NR	NR	NR
Waterhouse, 2022[46]	1L + 2L	15.3	NR	38	36.2 (15.9–not reached	NR	NR	NR	NR	NR	NR	NR	NR	NR
			6 months	NR	NR	NR	77.8	NR	NR	NR	NR	NR	NR	NR
			12 months	NR	NR	NR	71.9	NR	NR	NR	NR	NR	NR	NR
			24 months	NR	NR	NR	64.9	NR	NR	NR	NR	NR	NR	NR
			42 months¥	NR	27.3 (21.7–32.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gainor, 2017[60]	Mixed	38.4	NR	30	30∞ (12∞–not reached)	11.5	NR	NR	NR	NR	NR	NR	NR	NR
Shen, 2020[61]	1L	28.1	NR	30	Not reached	18.4 (6.4–30.3)	NR	NR	86.7	3.3	83.3	96.7	10	3.3
Zhang, 2021[47]	1L	28	NR	168	NR	18	NR	NR	85.7	0.6	85.1	97.1	11.3	2.9
Xu, 2020[48]	1L	24.9	NR	56	Not reached	14.9 (10.9–18.7)	NR	NR	83.9	0	83.9	96.4	12.5	3.6
Zheng, 2020[49]	1L	29	NR	OS/PFS: 56 RR: 51	60 (40.7–79.3)	23 (12.4–33.6)	NR	NR	64.7	2†	62.7†	94.1	29.4†	6
Studies included in the SLR by Vuong et al., 2020														
Capizzi, 2019[58]	1L + 2L	11.1	NR	8	Not reached	NA	NR	NA	62.5	25	37.5	62.5	0	37.5
Joshi, 2019[51]	Mixed	15.2	NR	16	Not reached	Not reached	NR	NR	93.8	12.5	81.3	93.8*	0	0.6
Li, 2018[52]	Mixed	31.9	NR	36	32.7	12.6	NR	NR	83.3*	0†	83.3	97.2*	13.9	2.8
Liu, 2019[53]	Mixed	NR	NR	35	41 (22.5–59.5)	11 (7.8–14.2)	NR	NR	71.4	0†	71.4	94.3	22.9	5.7
Masuda, 2019[54]	Mixed	35.5	NR	10	28.7	10 (5.1–27)	NR	NR	80	0†	80	100*	20	0

Study name Data source(s)	Line of therapy	Median follow-up (Months)	Timepoint / Assessment	Number of patients	Median (95% CI)		% of patients with event (95% CI)		ORR %	CR %	PR %	DCR %	SD %	PD %
					OS	PFS	OS	PFS						
(6.7–not reached)														
Mazières, 2015[55]	Mixed	NR	NR	30	NA	9.1	NA	NR	80	16.7	63.3	86.7	6.7	13.3
			12 months	NR	NA	NR	NA	44	NR	NR	NR	NR	NR	NR
Mehta, 2020[56]	1L + 2L	NR	NR	14	Not reached	Not reached	NR	NR	64.3	0†	64.3	85.7*	21.4	14.3
			12 months	NR	NR	NR	36.9	56.2	NR	NR	NR	NR	NR	NR
Zeng, 2018[57]	Mixed	NR	NR	19	NA	13.6	NA	NR	89.5	0	89.5	94.7*	5.3	5.3
Zhang, 2016[58]	≥2L	NR	NR	15	NA	9.8‡	NA	NR	80	6.7	73.3	90	20	0
Zhu, 2019[59]	Mixed	NR	NR	23	NA	14.5	NR	NR	56.5	0	56.5	78.3	21.7	21.7

Note: The proportion of patients with event for overall and progression-free survival was not reported.
*Reported data in Vuong *et al*., 2020.[44]
†Calculated based on the given data.
‡Original data is 294 days and adjusted to months format in Voung *et al*., 2020.[44]
¥Overall survival at 42 months reported as restricted mean survival time.
°The original data was in years—2.5 years and 1 year—and was converted to months.
Abbreviations: 1L: first line; 2L: second line; CR: complete response; DCR: disease control rate; MET: mesenchymal epithelial transition factor receptor; NSCLC: non-small cell lung cancer; NA: not applicable; NR: not reported; ORR: objective response rate; OS: overall survival; PD: progressive disease; PR: partial response; ROS1: proto-oncogene tyrosine-protein kinase 1; SD: stable disease; SACT: Systemic Anti-Cancer Therapy; ROS1: proto-oncogene tyrosine-protein kinase 1

B.3.11 Meta-analysis

Head-to-head evidence comparing crizotinib with entrectinib was not available, therefore, an indirect treatment comparison (ITC) was required to assess the clinical similarity of the treatments. A series of STCs were conducted for OS, PFS, DOR and ORR to estimate the relative efficacy of all relevant therapies (see Section B.3.12). MAICs were also conducted as sensitivity analyses for both PFS and OS.

B.3.12 Indirect and mixed treatment comparisons

The feasibility of conducting the ITC was investigated by reviewing the description of each trial, as well as comparing baseline characteristics based on the list of prognostic factors and treatment effect modifiers identified from the literature (list available in Appendix D, Table 10). STC was selected as the base case methodology over MAIC based on poor overlap of population in terms of ethnicity. A large proportion of patients in the crizotinib studies were Asian (82.2% in the pooled population of PROFILE 1001 and OxOnc). This constituted a challenge in applying weights to crizotinib patients to match the proportion of Asian patients from the entrectinib studies (45.3%). To avoid a highly reduced effective sample size, a STC was considered an appropriate approach, however a MAIC was conducted as a sensitivity analysis.

Details of the feasibility assessment are available in Appendix D, Section D.2.1. The description of the methodology of STC is available in Appendix D, Section D.2.2.

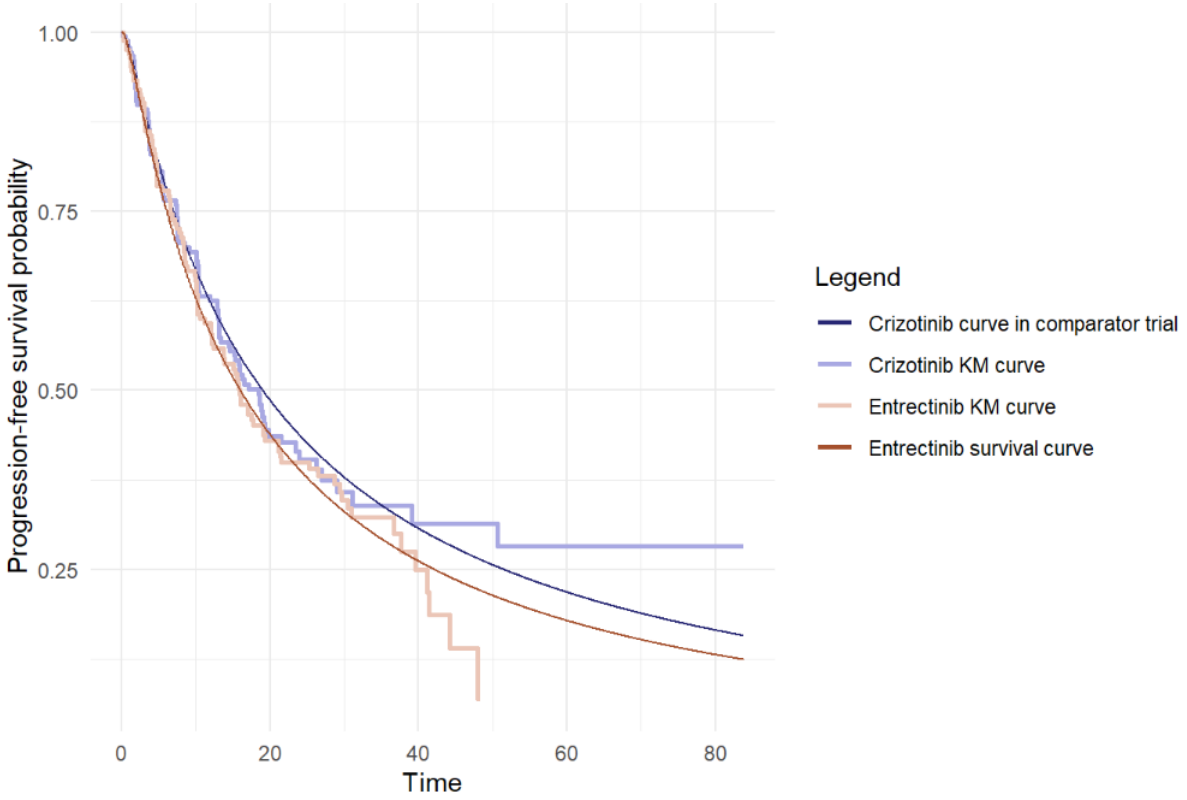
B.3.12.1 Progression-free survival

The seven standard parametric distributions (exponential, gamma, generalized gamma, Gompertz, log-logistic, log normal, and Weibull) were fitted to the PFS patient level data for crizotinib. The log normal distribution was selected based on its low Akaike information criterion (AIC) and Bayesian information criterion (BIC) values (indicating statistical goodness-of-fit) and visual inspection compared to the crizotinib Kaplan-Meier curve (see Appendix D, Table 12 and Appendix D, Figure 2).

A backward selection using the log normal survival distribution was performed to identify the variables to include in the model among age (over/under 54 years old), sex (male/female), ethnicity (Asian/ non-Asian), ECOG score (0/ 1 or more), smoking status and histological classification (adenocarcinoma, squamous cells, other). Three covariates were finally kept in the model: ECOG score, age, and smoking status.

The baseline characteristics from the pooled entrectinib trials of these three variables were applied to crizotinib results. The crizotinib curve was then fitted using the demographics of patients from entrectinib trials to recover the effect of crizotinib in a comparable population to entrectinib. The Kaplan-Meier curves and adjusted model are presented in Figure 6.

Figure 6. PFS Kaplan-Meier and adjusted survival model curves



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

The Kaplan-Meier curves cross multiple times prior to 40 months indicating little difference in effect. At 40 months, only 12 and 10 patients remained at risk in crizotinib and entrectinib arms respectively. Among the 10 entrectinib patients, 6 were censored and none remained at risk after 50 months. For crizotinib, ten patients were censored between 40 and 70 months, with two patients remaining at risk after 80 months. The gap in length of follow-up and high censoring rates after 40 months led to the separation of the Kaplan-Meier curves. The PFS HR crizotinib vs. entrectinib over time was computed (see Appendix D, Figure 4 and Appendix D, Table 15). [redacted] Results for PFS were favourable but non-significant for crizotinib, with confidence intervals including 1. The point estimates nearing 1 and the 95% CI confirm the clinically similar assumption for crizotinib and entrectinib with regards to the PFS data, with no statistically significant difference found.

B.3.12.2 Overall survival

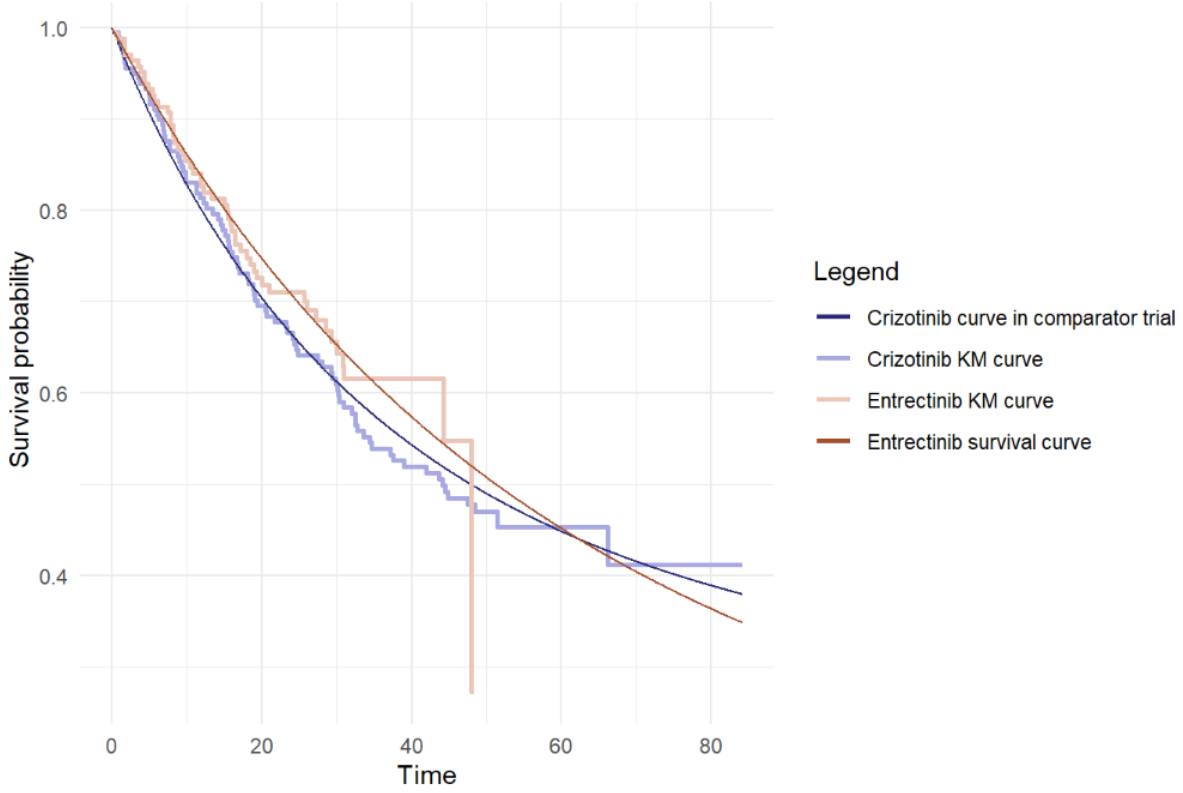
The seven standard parametric distributions were fitted to the OS patient level data for crizotinib. The Gompertz distribution was chosen based on its low AIC and BIC

values (indicating statistical goodness-of-fit) and visual inspection compared to the crizotinib Kaplan-Meier curve (see Appendix D, Table 16 and Appendix D, Figure 7).

A backward selection using the Gompertz survival distribution was performed to identify the variables to include in the model among age (over/under 54 years old), sex (male/female), ethnicity (Asian/ non-Asian), ECOG score (0/ 1 or more), smoking status and histological classification (adenocarcinoma, squamous cells, other). Three covariates were finally kept in the model: ECOG score, age, and smoking status.

The baseline characteristics from the pooled entrectinib trials of these three variables were applied to crizotinib results. The crizotinib curve was then fitted using the demographics of patients from entrectinib trials to recover the effect of crizotinib in a comparable population than entrectinib. The Kaplan-Meier curves and adjusted model are presented in Figure 7.

Figure 7. OS Kaplan-Meier and adjusted survival model curves



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

The survival curves of crizotinib and entrectinib cross around 60 months. The OS HR of crizotinib vs. entrectinib over time was computed and decreased over time (see Appendix D, Figure 9 and Appendix D, Table 19). On average, over seven years, the OS HR was estimated at [redacted]

[redacted]. Results for OS were overall similar between crizotinib and entrectinib with HR estimates crossing 1 over time and 95% CI including 1. The point estimates nearing 1 and the 95% CI confirm the clinically similar assumption for crizotinib and entrectinib with regards to the OS data, with no statistically significant difference found.

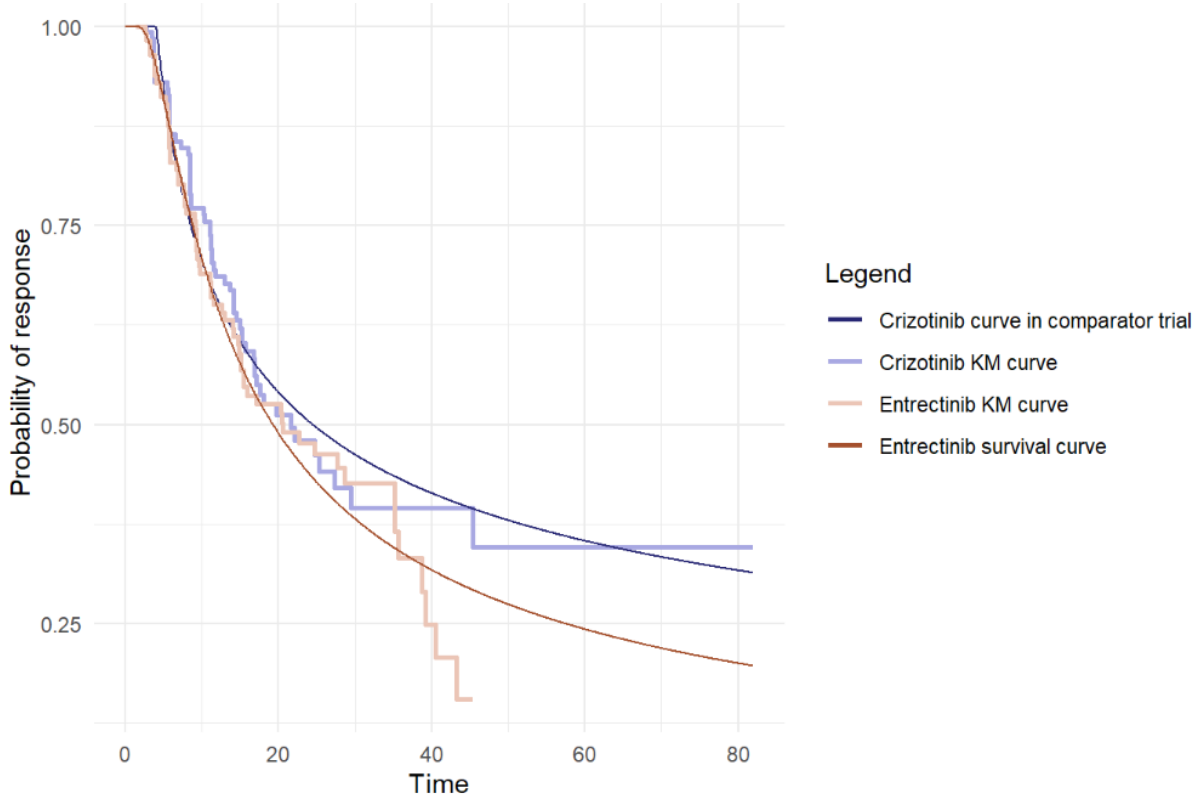
B.3.12.3 Duration of response

The seven standard parametric distributions were fitted to the DOR patient level data for crizotinib. The generalized gamma distribution was chosen based on its low AIC and BIC values (indicating statistical goodness-of-fit) and visual inspection compared to the crizotinib Kaplan-Meier curve (see Appendix D, Table 20 and Appendix D, Figure 12).

A backward selection using the generalized gamma survival distribution was performed to identify the variables to include in the model among age (over/under 54 years old), sex (male/female), ethnicity (Asian/ non-Asian), ECOG score (0/ 1 or more), smoking status and histological classification (adenocarcinoma, squamous cells, other). Two covariates were finally kept in the model: ECOG score and age.

The baseline characteristics from the pooled entrectinib trials of these two variables were applied to crizotinib results. The crizotinib curve was then fitted using the demographics of patients from entrectinib trials to recover the effect of crizotinib in a comparable population than entrectinib. The Kaplan-Meier curves and adjusted model are presented in Figure 8.

Figure 8. DOR Kaplan-Meier and adjusted survival model curves



Abbreviations: DOR: duration of response; KM: Kaplan-Meier

The DOR HR for crizotinib vs. entrectinib over time was computed. On average, over seven years, [redacted] (see Appendix D, Figure 14 and Appendix D, Table 23). Results for DOR were favourable but non-significant for crizotinib, with 95% confidence intervals crossing 1. These results suggest overall clinical similarity between crizotinib and entrectinib with regards to DOR, with no statistically significant difference found.

B.3.12.4 Overall response rate

A backward selection using a generalized linear model was performed to identify the variables to include in the model among age (over/under 54 years old), sex (male/female), ethnicity (Asian/non-Asian), ECOG score (0/1 or more), smoking status and histological classification (adenocarcinoma, squamous cells, other). Three covariates were finally kept in the model: ECOG score, smoking status, and age.

The baseline characteristics from the pooled entrectinib trials of these three variables were applied to crizotinib results. The crizotinib curve was then fitted using the Company evidence submission: Crizotinib for treating ROS1-positive advanced non-small cell lung cancer.

demographics of patients from entrectinib trials to recover the effect of crizotinib in a comparable population than entrectinib.

In a trial with the same patients as the entrectinib pooled trials (n=168), [redacted] while the actual pooled clinical trials corresponding to entrectinib had 114 patients with an ORR (67.9%). [redacted] (see Appendix D, Section D.2.3.4). These results confirm the clinical similarity between crizotinib and entrectinib as the 95% confidence intervals cross 1, suggesting no statistically significant differences between the two arms in regards to ORR.

B.3.12.5 Safety analysis (adverse events)

An analysis of discontinuations due to TRAEs and due to treatment-emergent AEs (TEAEs) has been investigated. Due to the low number of events for AEs leading to discontinuation, it has been concluded that a model with too few patients only in the crizotinib arm would not converge and the analysis of safety was thus limited to a descriptive assessment in section B.3.13 below.

B.3.12.6 Uncertainties in the indirect and mixed treatment comparisons

One of the main limitations of the STC is the potential bias introduced when choosing the survival parametric distribution. Indeed, parametric distributions assume a specific form for the distribution of survival data. If the true distribution of survival data is different (over- or under-estimation, heterogeneity inherent to the clinical trial not sufficiently represented by the extrapolation, etc.) from that assumed by the model, this can lead to a bias in the extrapolated results.[62]

To ensure the robustness of the analysis, a MAIC was conducted as a sensitivity analysis on PFS. (see Appendix D, Section D.2.3.5)

The main inclusion and exclusion criteria were similar for the two trials (pooled crizotinib and pooled entrectinib trials), except for number of prior regimens, major surgery radiation within 2 weeks and use of drug known as strong CYP3A4 inhibitors:

- 3 prior treatments maximum were allowed in OxOnc trials whereas no restriction was made for the rest of the trials (PROFILE 1001 for crizotinib, ALKA-372-001, STARTRK-1 and STARTRK-2 for entrectinib)
- Having a major surgery, radiation therapy within 2 weeks was an exclusion criterion for ALKA-372-001 and PROFILE 1001
- Use of drug that are known as strong CYP3A4 inhibitors was an exclusion criterion for OxOnc and PROFILE 1001

The list of included covariates considered for the matching included the following prognostic factors and treatment effect modifiers (identified in Appendix D, Table 10):

- Age (≥54 years old / <54 years old)
- Sex (male/female)
- Smoking status (previous smoker/ never smoker)
- Ethnicity (Asian / not Asian)
- ECOG PS (0 / 1 or more)
- Histological classification (adenocarcinoma, squamous cells, other)

B.3.12.6.1 MAIC using all covariates of interest

A MAIC analysis adjusting weights on all identified covariates of interest (age group, race: Asian, ECOG, sex, smoking status, Histological classification) was performed.

The base-case MAIC led to an effective sample size (ESS) of 83.3 patients (46.3% of the original sample size for crizotinib). It resulted in a HR of [redacted] for PFS of crizotinib, and of [redacted] for OS. The confidence intervals contain 1 which means we cannot reject the null hypothesis of no differences in OS between the two treatments (i.e. HR=1). However, since the assumptions of proportional hazard are not fully verified, the interpretation of this finding should be approached with caution and critical analysis.

B.3.12.6.2 MAIC excluding the ethnicity covariate

Because of the imbalance of the crizotinib and entrectinib populations in proportions of Asian/non-Asian patients, the non-Asian patients had a disproportionate influence in the reweighted population. This is why a second MAIC analysis has been performed, this time excluding the Race covariate.

The MAIC without race covariate led to an ESS of 158.2 patients (87.9% for the original sample size) for crizotinib. Distribution of weights as well as analysis of the final Kaplan-Meier curve and its corresponding proportional hazard assumption test are available in Appendix D, Section D.2.3.5.

The MAIC without race led to a HR for PFS of crizotinib vs entrectinib of [redacted]

This value is comparable to the values of HR over time obtained in the STC analysis of PFS, where the HR between crizotinib and entrectinib is reasonably constant over time, around a value of [redacted]_For OS, the value obtained through the MAIC is in the range of the STC results [redacted] Overall these results, as well as the consistency with the results of STC, indicate that it is reasonable and conservative to conclude that crizotinib and entrectinib are clinically similar in terms of OS and PFS.

B.3.13 Adverse reactions

AEs in patients treated for ROS1-positive NSCLC were reported in six studies (PROFILE 1001, METROS, EUCROSS, OxOnc, STARTRK-2, ALKA-372-001, STARTRK-1, STARTRK-2). Among those six studies (ten publications), four studies focused on patients who were treated with crizotinib, while the remaining two focused on entrectinib. [22–26,29,32,33,36,37,39] Detailed information can be found in Table 18, Table 19, and Table 20.

Almost all patients receiving crizotinib had at least one TRAE, ranging from 100% of patients in PROFILE 1001 and METROS to 97% of patients in EUCROSS (Table 18) with the majority being grades 1 and 2.[26,29] EUCROSS and METROS reported any-grade severe AEs (SAE) in 12.5% and 14.7% of trial participants, respectively.[26,29] For patients receiving crizotinib, the most frequently reported TRAEs of any grade were vision disorders (ranging from 23%–87% of patients), fatigue (12%–58%), and gastrointestinal AEs such as vomiting (27%–38%), nausea (40–51%), diarrhoea (27%–56%), and constipation (15%–34%) (Table 19). EUCROSS reported the highest rate of patients with any type of grade ≥3 AE (74%) after receiving crizotinib treatment.[29] In the PROFILE 1001 updated analysis, there was no significant increase in all grade TRAEs from the original analysis after a median follow-up extension of 46.2 months.[22,23] Grade 4 and 5 AEs were less frequently reported in crizotinib clinical studies with OxOnc and EUCROSS each reporting grade 4 or 5 AEs in 3% of trial participants.[24,29]

Similar to the crizotinib clinical studies, nearly all patients (93.3%) receiving entrectinib experienced at least one TRAE of any grade (Table 18).[37] Serious TRAEs were reported in two different publications covering the pooled analysis of ALKA-372-001, STARTRK-1, and STARTRK-2 at 14.7% (33/224 patients) and 11% (23/210 patients), respectively.[36,37] In STARTRK-2, all 23 patients receiving entrectinib experienced TRAE of any grade and 4 out of 23 patients (17.4%) reported treatment-related SAEs.[33] In entrectinib studies the most commonly observed TRAEs (STARTRK-2) were gastrointestinal issues, with constipation occurring in 52.2% of patients, diarrhoea in 40%, and nausea in 31.1% of patients (Table 19).[32] Dysgeusia was observed as AEs of any grade with its highest rate occurring among patients who received entrectinib, affecting 43.3% and 40.6% of patients.[36,37] No grade 5 AEs were reported in entrectinib studies for patients with ROS1-positive NSCLC.

Table 18. Adverse events (all-cause, grade 3/4, treatment-related) in patients with ROS1-positive NSCLC

Adverse events in ROS1-positive NSCLC	Crizotinib				Entrectinib		
	PROFILE 1001 (NCT00585195)	OxOnc (NCT01945021)	METROS (NCT02499614)	EUCROSS (NCT02183870)	STARTRK-2 (NCT02568267)	ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)	
	Shaw, 2019[23]* N=53	Wu 2022[25] N=127	Landi, 2019[26] N=26	Michels 2019[29] N=34	Paz-Ares, 2021[32] N=180	Drilon, 2022[36]† N=224	Dziadziuszko, 2021[37]† N=210
Median follow-up (months)	62.6	56.1 (95% CI: 52.1−59.4)	21 (95% CI, 19.0−24.5)	20.6	16.8 (range, 0.1−37.8)	29.1 (IQR, 21.8−35.9)	15.8 (IQR, 10.4−22.9)
Any grade AE, n (%)							
Any AEs	53 (100)	TEAE: 127 (100)	26 (100)	33 (97)	180 (100)	NR	208 (99)
Any SAEs	NR	NR	6 (12.5) ‡	5 (14.7)¥	75 (41.7)	NR	NR
Treatment-related AEs	53 (100)§	124 (97.6)	26 (100)	33 (97)	180 (100)	NR	196 (93.3)
Treatment-related SAEs	NR	11‡ (8.7)	NR	5 (14.7)¥	NR	33 (14.7)	23 (11)
Grade ≥3 AEs, n (%)							
Any AEs	3: 19 (36) 4: 0 (0) 5: 0 (0)	NR	NR	3: 19 (56) 4: 0 (0) 5: 6 (18)	120 (66.7)	NR	NR
Any SAEs	NR	NR	NR	3: 3 events (n NR) ¥ 4: 0 (0) 5: 1 (3)‡	NR	NR	NR
Treatment-related AEs	NR	3: 35 (27.6) 4: 5 (3.9) 5: 1 (0.8)	NR	3: 8 (24) 4: 0 (0) 5: 1 (3)	68 (37.8)	NR	NR
Treatment-related SAEs	NR	NR	NR	3: 3 events (n NR) ¥ 4: 0 (0) 5: 1 (3)‡	NR	NR	NR

*Shaw *et al*., 2019 updated the data for the population at the data cut-off (30 June 2018), whereas the data cut-off date was April 11, 2014, in Shaw *et al*., 2014.
†The clinical cut-off was 31 August 2020 in Drilon *et al*., 2022, and 1 May 2019 for Dziadziuszko *et al*., 2021
‡ calculated value
§ All 53 patients experienced at least one treatment-related adverse event.
¥ Eight treatment-related serious adverse events occurred in five patients. This comprised of two grade 1, two grade 2, three grade 3, and one grade 5 event.
Abbreviations: AE: adverse event, NSCLC: non-small cell lung cancer; SAE: serious adverse event, TEAE: treatment-emergent adverse event

Table 19. Any grade treatment-related adverse events in ≥10% of all safety-evaluable patients, as reported in the included studies

Treatment-related adverse events (Any grade, with majority grade 1-2)	Crizotinib					Entrectinib ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)**	
	PROFILE 1001 (NCT00585195) Shaw, 2019[23]* N=53	OxOnc (NCT01945021) Wu, 2022[25] N=127	METROS (NCT02499614) Landi, 2019[26] N=26	EUCROSS (NCT02183870) Michels, 2019[29] N=34	STARTRK-2 (NCT02568267) Paz-Ares, 2021[32] N=180	Dziadziuszko, 2021[37] N=210	Drilon, 2022[36] N=224
Vision disorder	46 (**87**)	61 (**48.0**)	6 (23)	22 (**65**)	NR	NR	Blurred vision: 12 (5.4)
Nausea	27 (**51**)	53 (**41.7**)	12 (46)	14 (**41**)	56 (31.1)	39 (18.6)	45 (20.1)
Oedema	25 (**47**)	34 (26.8)	Peripheral: 13 (50)	17 (**50**)	NR	Peripheral: 38 (18.1) Generalised: 5 (2.4)	Peripheral: 48 (21.4) Generalised: 5 (2.2)
Diarrhoea	24 (**45**)	53 (**41.7**)	7 (27)	19 (**56**)	72 (**40.0**)	56 (26.7)	68 (30.4)
Respiratory symptoms	NR	NR	Cough, pneumonitis, dyspnoea: 11 (42)	NR	Dyspnoea: 57 (31.7) Exertional dyspnoea: 3 (1.7)	NR	NR
Vomiting	20 (38)	43 (33.9)	7 (27)	11 (32)	41 (22.8)	30 (14.3)	35 (15.6)
Elevated transaminases	19 (36)	85 (**66.9**)	7 (27)	AST: 9 (26) ALT: 12 (35)	NR	AST: 25 (11.9) ALT: 23 (10.9)	AST: 27 (12.0) ALT: 26 (11.6)
Constipation	18 (34)	41 (32.3)	NR	5 (15)	94 (**52.2**)	66 (31.4)	71 (31.7)
Pain	NR	NR	8 (31)	NR	NR	NR	NR
Increased weight	NR	NR	NR	NR	NR	60 (28.6)	77 (34.4)
Bradycardia	11 (21)	14 (11)	NR	16 (**47**)	NR	NR	NR
Fatigue	11 (21)	15 (11.8)	15 (58)	Asthenia/ fatigue: 6 (18)	NR	63 (30.0)	62 (27.7)
Blood creatine increased	NR	25 (19.7)	0 (0)	7 (21)	NR	39 (18.6)	49 (21.8)
Dizziness	10 (19)	NR	NR	5 (15)	NR	73 (34.8)	83 (40.0)
Dysgeusia	10 (19)	17 (13.4)	NR	4 (12)	NR	91 (**43.3**)	91 (**40.6**)
Anorexia	NR	NR	5 (19)	NR	NR	NR	NR
Paraesthesia	NR	NR	NR	NR	NR	39 (18.6)	41 (18.3)
Myalgia	NR	NR	NR	NR	NR	35 (16.7)	37 (16.5)
Hypophosphatemia	9 (17)	NR	NR	NR	NR	4 (1.9)	3 (1.3)
Decreased appetite	8 (15)	22 (17.3)	NR	NR	23 (12.8)	NR	11 (4.9)
Leukopenia	Neutropenia: 8 (15)	Leukopenia: 33 (26.0) Neutropenia: 43 (33.9)	Neutropenia: 2 (8)	Leukopenia/ neutropenia: 11 (32)	NR	Neutropenia: 9 (4.3)	Neutropenia: 10 (4.4)
Abdominal pain	NR	NR	NR	5 (15)	NR	NR	NR

Treatment-related adverse events (Any grade, with majority grade 1-2)	Crizotinib					Entrectinib	
	PROFILE 1001 (NCT00585195)	OxOnc (NCT01945021)	METROS (NCT02499614)	EUCROSS (NCT02183870)	STARTRK-2 (NCT02568267)	ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)**	
	Shaw, 2019[23]* N=53	Wu, 2022[25] N=127	Landi, 2019[26] N=26	Michels, 2019[29] N=34	Paz-Ares, 2021[32] N=180	Dziadziuszko, 2021[37] N=210	Drilon, 2022[36] N=224
Anaemia	NR	NR	2 (8)	5 (15)	NR	24 (11.5)	30 (13.4)
Rash	7 (13)	NR	NR	NR	NR	16 (7.6)	19 (8.4)
Blood AP increased	NR	13 (10.2)	NR	4 (12)	NR	NR	NR
Arthralgia	NR	NR	NR	NR	NR	19 (9.1)	27 (12.1)
Dysphagia	NR	NR	NR	NR	NR	NR	23 (10.3)

*Shaw *et al*., 2019 updated the data for the population at the data cut-off (30 June 2018), whereas the data cut-off date was 11 April 2014, in Shaw *et al*., 2014.
****** The clinical cut-off was 31 August 2020, in Drilon *et al*., 2022, and 1 May 2019, for Dziadziuszko *et al*., 2021, Tan *et al*., 2020 and Liu *et al*., 2020.
Abbreviations: AE: adverse event; ALT: alanine transaminase AST: aspartate transaminase; ATE: arterial thrombotic event; MET: mesenchymal epithelial transition; ROS1: proto-oncogene tyrosine-protein kinase 1; SAE: serious adverse event; VTE: venous thrombotic event.

Table 20. Grade ≥3 treatment-related adverse events in ≥1% of all safety-evaluable patients, as reported in the included studies

Treatment-related adverse events (grade ≥3)	Crizotinib								Entrectinib				
	PROFILE 1001 (NCT00585195)		OxOnc (NCT01945021)		METROS (NCT02499614)	EUCROSS (NCT02183870)			STARTRK-2 (NCT02568267)	ALKA-372-001, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267)**			
	Shaw, 2019[23]* N=53		Wu, 2022[25] N=127		Landi, 2019[26] N=26	Michels, 2019[29] N=34			Paz-Ares, 2021[32] N=180	Dziadziuszko, 2021[37] N=210		Drilon, 2022[36] N=224	
	3	≥4	3	4	3-4	3	4	5	≥3	3	4	3	4
Hypophosphatemia	8 (15)	No ≥4 TRAEs	NR	NR	NR	NR	NR	NR	NR	1 (0.5)	0 (0)	NR	NR
Leukopenia	NR		3 (2.4)	0 (0)	NR	1 (3)	0 (0)	0 (0)	NR	NR	NR	NR	NR
Neutropenia	5 (9)		12 (9.4)	3 (2.4)	1 (4)				NR	4 (1.9)	0 (0)	5 (2.2)	0 (0)
Increased weight	NR		NR	NR	NR	NR	NR	NR	NR	17 (8.1)	0 (0)	25 (11.2)	0 (0)
Vomiting	2 (4)		NR	NR	0 (0)	1 (3)	0 (0)	0 (0)	NR	2 (1.0)	0 (0)	2 (0.9)	0 (0)
Elevated transaminases	2 (4)		7 (5.5)	2 (1.6)	0 (0)	AST: 0 (0) ALT: 1 (3))	AST: 0 (0) ALT: 0 (0)	AST: 0 (0) ALT: 0 (0)	NR	AST: 5 (2.4) ALT: 7 (3.3)	AST: 0 (0) ALT: 0 (0)	AST: 4 (1.8) ALT: 0 (0)	AST: 7 (3.1) ALT: 0 (0
Nausea	1 (2)		2 (1.6)	0 (0)	2 (8)	1 (3)	0 (0)	0 (0)	NR	2 (1.0)	0 (0)	2 (0.9)	0 (0)
Decreased appetite	1 (2)		1 (0.8)	0 (0)	NR	NR	NR	NR	NR	NR	NR	0 (0)	0 (0)
Fatigue	0 (0)		2 (1.6)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)	NR	1 (0.5)	0 (0)	1 (0.4)	0 (0)
Oedema	0 (0)		1 (0.8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	NR	General: 1 (0.5) Peripheral: 1 (0.5)	0 (0)	General: 1 (0.4) Peripheral: 1 (0.4)	0 (0)
Diarrhoea	0 (0)		1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR	6 (2.9)	0 (0)	6 (2.7)	0 (0)
Bradycardia	0 (0)		2 (1.6)	0 (0)	NR	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR
Pain	NR		NR	NR	1 (4)	NR	NR	NR	NR	NR	NR	NR	NR
Respiratory symptoms	NR		NR	NR	1 (4)	NR	NR	NR	NR	NR	NR	NR	NR
Dysgeusia	0 (0)		0 (0)	0 (0)	NR	1 (3)	0 (0)	0 (0)	NR	1 (0.5)	0 (0)	1 (0.4)	0 (0)
Pulmonary embolism	NR		NR	NR	NR	0 (0)	0 (0)	1 (3)	NR	NR	NR	NR	NR
Neutrophil count decreased	NR		NR	NR	NR	NR	NR	NR	NR	5 (2.4)	0 (0)	7 (3.1)	0 (0)

*Shaw *et al*., 2019 updated the data for the population at the data cut-off (30 June 2018), whereas the data cut-off date was 11 April 2014, in Shaw *et al*., 2014.
**The clinical cut-off was 31 August 2020, in Drilon *et al*., 2022, and 1 May 2019, for Dziadziuszko *et al*., 2021.
†This study reported the AEs in grade 3 and 4.
Abbreviations: AE: adverse event; ALT: alanine transaminase AST: aspartate transaminase; ATE: arterial thrombotic event; MET: mesenchymal epithelial transition; ROS1: proto-oncogene tyrosine-protein kinase 1; SAE: serious adverse event; VTE: venous thrombotic event.

B.3.13.2 Treatment discontinuations due to adverse events

Discontinuation related to AEs, resulting in permanent treatment discontinuations, was described in three crizotinib studies, PROFILE 1001 (2% due to TRAEs), OxOnc (2.4% due to TRAEs) and AcSé (8.1% due to AEs).[22,25,31] In two entrectinib studies, discontinuation due to TRAEs ranged from 6.6% to 21.7%.[32,39]

Table 21. Treatment discontinuations due to adverse events

Tx	Study name Data source(s)	Patient group	Median follow-up (months)	Number of patients	Treatment discontinuations due to AEs, n (%)
Crizotinib	PROFILE 1001 Shaw, 2014[22]	ROS1-positive NSCLC	16.4	50	Due to TRAE: 1 (2)
	PROFILE 1001 Shaw, 2019[23]		62.6	53	NR
	OxOnc Wu 2022[25]	ROS1-positive NSCLC	56.1	127	Due to TRAE: 3 (2.4)
	EUCROSS Michels 2019[29]	ROS1-positive NSCLC	20.6	34	NR
	AcSé Moro-Sibilot 2019[31]	ROS1-positive NSCLC	60	37	Due to toxicity: 3 (8.1)
Entrectinib	STARTRK-2 Paz-Ares, 2021[32]	ROS1-positive NSCLC, **safety population**	>12 months	180	NR
	STARTRK-2 Murakami 2022[33]	ROS1-positive NSCLC – **Japanese subgroup**	>12 months	23	Due to TRAE: 5 (21.7)
	ALKA-372-001, STARTRK-1, STARTRK-2 Tan, 2020[39]	**Subgroup:** Asian patients with ROS1-positive NSCLC*	19.8	41	Due to TRAE: NR (6.6)

* The clinical cut-off was 1 May 2019 for Tan *et al*., 2020.
Abbreviations: AE: adverse events; NR: not reported; NSCLC: non-small cell lung cancer; ROS1: proto-oncogene tyrosine-protein kinase 1; TRAE: treatment-related adverse event

B.3.14 Conclusions about comparable health benefits and safety

Overall, crizotinib and entrectinib exhibited substantially similar median OS and PFS in their respective available studies identified in the SLR. Crizotinib-treated patients demonstrated a median OS of 17.2–51.4 months, while those on entrectinib had a median OS ranging from 28.3–47.8 months. Median PFS for crizotinib ranged from 5.5–22.8 months, compared to 12.5–15.7 months for entrectinib. Only two studies (PROFILE 1001 and OxOnc) reported mature OS data; the remaining six studies reported immature OS data, indicating the need for longer follow up. Furthermore, both crizotinib and entrectinib displayed comparable ORRs (ranging from 65–72% and 62.5–83.9%, respectively) and DCRs, with a median DOR of 21.4 months (95% CI, 12.7–30.1) for crizotinib compared to 20.5 months (95% CI, 14.8–34.8) for entrectinib.

A series of STCs were run for PFS, OS, DOR, and ORR between crizotinib and entrectinib (Section B.3.12). These STCs provided the relative treatment effect over time for time-to-event outcomes, with HRs estimated at specific timepoints, while ORs were obtained for the ORR outcome. Results were overall similar between crizotinib and entrectinib. For time-to-events outcomes, results were reasonably constant over time [redacted] for PFS, with confidence intervals including 1. For OS and DOR, HR estimates crossed 1 over time, with confidence intervals including 1 [redacted]. For binary outcome ORR, the OR also suggested similarity between crizotinib and entrectinib with a value of [redacted]

The base-case MAIC to assess uncertainty on PFS results revealed a HR for crizotinib vs entrectinib at [redacted] The CI contains 1, suggesting non-statistically significant differences and clinical similarity between crizotinib and entrectinib. However, since the assumptions of proportional hazard are not fully verified, the interpretation of this finding should be approached with caution and critical analysis. The second MAIC without race as an adjustment covariate resulted in a HR for PFS of crizotinib vs entrectinib of [redacted] Results for OS were [redacted] for the MAIC with all covariates and [redacted] for the MAIC without race. Similar interpretation as for PFS results applies.

In terms of safety and tolerability, TRAEs were frequent (>90% incidence) for both crizotinib and entrectinib, with similar discontinuation rates of 2%-8.1% and 6.6%-21.7%, respectively, related to AEs (Section B.3.13). Patients treated with crizotinib frequently experienced vision disorders and fatigue, while dysgeusia was commonly associated with entrectinib. Gastrointestinal issues occurred frequently with both crizotinib (vomiting, nausea, diarrhoea, constipation) and entrectinib (constipation, diarrhoea, nausea).

Data gaps included limited reporting of QoL outcomes, with predominantly insignificant results when available. Time to response and response rate data for entrectinib were lacking, requiring further research. Heterogeneity across studies, including patient populations and follow-up durations, was observed.

It is essential to acknowledge that the rarity of this specific tumour contributes to a less robust evidence base, posing challenges in conducting large randomised controlled trials. Despite these limitations, evidence demonstrating the relative treatment effects of crizotinib and entrectinib are comparable, suggesting equivalence in delaying disease progression and extending survival.

Furthermore, RWE data from the SACT database and market share data from the Ipsos Oncology Monitor 2024 showed that despite the introduction of entrectinib, crizotinib usage persisted with a consistent number of new patients initiated on crizotinib demonstrating its strong position in addressing clinical need.[21] In addition to this, clinical experts confirmed that crizotinib continues to be a sought-after treatment option for patients with ROS1-positive NSCLC, with proven efficacy.

Overall, the data supporting the administration of tyrosine kinase inhibitors represents a transformative shift in clinical practice compared to the previous standard of care, which involved chemotherapy.

Strengths and limitations of the clinical evidence base for crizotinib

Since the original submission to NICE in 2017 (TA529), the clinical evidence base of crizotinib has grown extensively.[2] PROFILE 1001 supported the application for the crizotinib EU market authorisation, received on 25 August 2016. The EMA recognised the strengths of this study despite the limited evidence for crizotinib in ROS1-positive NSCLC, and it was used as the main evidence for the approval of crizotinib for ROS1-positive NSCLC due to the rarity of the condition.[63]

While to this date there are no RCTs available, since the inception of PROFILE 1001, four additional studies (METROS, EUCROSS, AcSé, OxOnc) have been published adding to the clinical evidence of crizotinib. All four studies have been conducted as phase 2 studies, having covered additional subgroups such as patients who received at least one prior chemotherapy line or had advanced or metastatic NSCLC. While PROFILE 1001 covered patient populations in Australia, South Korea and the USA, METROS, EUCROSS and AcSé added clinical evidence on European populations (Italy, France, German, Spain, Switzerland) and OxOnc provided evidence on patient populations in China, Japan, and Taiwan. Furthermore, the included studies had a low risk of bias across all domains of the ROBINS-I quality assessment checklist, and a low confounding bias was anticipated.

In addition, the evidence from published clinical studies is also supported by RWE studies which showed similar results in OS compared to the clinical setting and thus support the maintenance of crizotinib alongside entrectinib in the current ROS1-positive NSCLC treatment guidelines.[53,60]

All of the studies included in this submission are highly relevant to the decision problem as they include patients with confirmed ROS1-positive advanced NSCLC. Furthermore, both treatment-naïve and treatment-experienced ROS1-positive NSCLC patients were included which further adds to the applicability of the clinical findings to the general population of interest as since 2018, NHSE has a strong preference for ROS1-positive patients to be treated with crizotinib as first-line therapy for advanced NSCLC.[17] Lastly, many of the included studies cover various smoking behaviour in patients, including 'never smokers'. As stated in the 2017 NICE crizotinib submission (TA529),[2] UK clinical experts expressed that the relevant patient population includes younger patients and never-smokers, supported by a study by Viola *et al*., 2016,[64] further confirming the relevance of the clinical evidence presented.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

The reimbursement of crizotinib is not expected to change the service provision or add additional burden or costs to the service. Crizotinib and the comparator entrectinib are both oral medications, therefore there are no differences expected in the resources needed to administer each drug as the only administration costs incurred are for delivery and dispensing (Section B.4.2.2). No differences are expected for treatment monitoring. Costs for AE management for both drugs are expected to be low, as the only AE of grade ≥3 occurring in at least 5% of patients and requiring medical resource use was hypophosphatemia during crizotinib treatment. As such no meaningful differences are expected (Section B.3.13).

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost comparison analysis has been conducted to evaluate the expected costs in clinical practice compared with entrectinib under the assumptions of similar clinical efficacy and safety. The cost comparison model estimates the total costs across the selected time horizon, disaggregated by cost type. Cost inputs considered in the base-case analysis comprised drug acquisition costs, administration costs, drug monitoring costs, and AE management costs.

Costs were calculated over a lifetime horizon defined in the base-case as 20 years, with the model allowing flexibility for up to a maximum of 40 years. The base case time horizon was considered appropriate and long enough to capture the difference in costs of the drugs being compared as per the NICE reference case.[65] Future costs were not discounted in the base case as it is not required in a cost-comparison analysis, per the NICE cost comparison guidance.[66] However, the model allows the option. Additional details of cost sources are available in Appendix G and Appendix H.

B.4.2.2 Intervention and comparators' acquisition costs

Unit costs were sourced from the 2021/2022 NHS reference costs[67] and the British National Formulary (BNF).[68] Drug acquisition list costs for packs of crizotinib and entrectinib are provided in Table 22 and the analyses included the Patient Access Scheme (PAS) applicable for crizotinib. It is worth noting this analysis does not incorporate the unknown PAS applicable to entrectinib, due to its confidentiality. The dose and posology of each treatment were taken from their respective SmPC.[5,69] Details such as the source information for drug administration are included in Appendix H.

Table 22. Acquisition costs of the intervention and comparator technologies used in the cost comparison analysis

	Crizotinib	Entrectinib
Pharmaceutical formulation	250 mg tablets, 60 per pack	200 mg tablets, 90 per pack
(Anticipated) care setting	Secondary	Secondary
Acquisition cost (excluding VAT)	£4,689 list price [redacted]	£5,160 list price
Method of administration	Oral	Oral
Doses	250 mg	600 mg
Dosing frequency	Twice daily taken continuously	Once daily
Dose adjustments	200 mg reduced dose	Up to two 200 mg dose reductions
Average length of a course of treatment	Continuous until disease progression, clinical deterioration, or unacceptable toxicity effects.	Continuous until disease progression, clinical deterioration, or unacceptable toxicity effects.
Average cost of a course of treatment (acquisition costs only)	£57,088.58 per year (list) [redacted]	£62,823 per year
Patient access scheme unit price (cost code)	First cycle: £197.25 Subsequent cycles: £14.59	First cycle: £197.25 Subsequent cycles: £14.59

Abbreviations: PAS, patient access scheme

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Resource utilisation (monitoring costs) was applied for the portion of time patients received treatment (Table 23). Monitoring frequency data was based on TA529, with the costs updated to reflect the most recent reference costs. This resource utilisation data was considered the best available data as it has been reviewed and accepted by NICE in several appraisals including TA643.[19] In line with both TA529 and TA643, it was assumed both crizotinib and entrectinib are managed the same and thus require the same resource use costs.

Table 23. Resource utilisation and monitoring costs

Resource required	% patients per month	Frequency per month	Total frequency per cycle	Unit cost	Source	Total cost per cycle
Outpatient visit	100%	0.75	0.75	£205.78	NHS Reference costs 2021/22, outpatient attendance data -medical oncology (370)	£154.34

Resource required	% patients per month	Frequency per month	Total frequency per cycle	Unit cost	Source	Total cost per cycle
GP visit	10%	1	0.10	£35.00	PSSRU 2022 - Clinic consultation lasting 9.22 minutes without qualification costs	£3.50
Cancer nurse	20%	1	0.20	£119.00	NHS Reference costs 2021/22, specialist nursing. cancer related, adult face to face (N10AF)	£23.80
Complete blood count	100%	0.75	0.75	£2.96	NHS Reference costs 2021/22, Haematology (DAPS05)	£2.22
Bio chemistry	100%	0.75	0.75	£1.55	NHS Reference costs 2021/22, Clinical Biochemistry (DAPS04)	£1.16
CT scan	30%	0.75	0.225	£160.38	NHS Reference costs 2021/22, computerised tomography scan of three areas, with contrast (RD26Z)	£36.09
Chest X ray	100%	0.75	0.75	£38.28	NHS Reference costs 2021/22: Direct Access plain film (DAPF)	£28.71
						£249.81

Abbreviations: GP, general practitioner; NHS, National Health Services; PSSRU, Personal Social Services Research Unit

B.4.2.4 Adverse reaction unit costs and resource use

Following the established practice in health economic modelling, only grades 3 and 4 AEs occurring in greater than 5% of patients were included in the base case cost comparison model (Table 24). However, because only one AE occurred in entrectinib treated patients above this rate, and management of this AE incurs no cost, a scenario analysis was performed wherein management costs for AEs occurring in at least 2% of patients were considered (Section B.4.4). AE management costs were applied as a one-off cost in the first cycle.

Table 24. AE management costs of grades 3 and 4 AEs (incidence >5%)

Treatment	Adverse event	Incidence	Resource use required	Cost	Source	Total
Crizotinib	Hypophosphatemia	15.09%	1 hospitalisation day	£535.97	NHS reference costs 2021/22; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N	**£80.90**
	Neutropenia	9.43%	Managed by dose reduction	£0.00	Managed by dose reduction[2,19]	
Entrectinib	Increased weight	11.16%	No hospitalisation required	£0.00	Assumed to incur no costs (as per TA529 assumption)	**£0.00**

B.4.2.5 Miscellaneous unit costs and resource use

No further unit costs and resource use, such as costs for genetic testing, were considered relevant or different between the comparator arms, given the clinical similarity in efficacy assumption.

B.4.2.6 Clinical input and assumptions

B.4.2.6.1 Treatment duration

In accordance with their respective marketing authorisations, both crizotinib and entrectinib are administered until disease progression or unacceptable toxicity.[5,69] PFS was therefore considered an appropriate proxy for modelling treatment duration. The assumption that PFS is broadly similar to treatment duration has been accepted in several previous appraisals, including TA643 and TA836.[19,70] As described in Section B.3.12, the STC demonstrated similar efficacy between crizotinib and entrectinib, with non-significant differences in PFS (HR of 0.88 (95% CI, 0.58-1.18) after one year, and 0.90 (95% CI, 0.54-1.26) from the fourth to seventh year). As such the PFS for entrectinib was assumed to be equal crizotinib, and the PROFILE 1001 PFS data was used to model treatment duration for both arms. [23]

To model treatment duration beyond the observed data from PROFILE 1001, parametric distributions were fitted to the latest PFS data in line with the NICE DSU guidance.[71] Model selection was based on the following considerations:

- Ranking distributions based on their statistical goodness-of-fit to the observed data according to AIC and BIC;
- A visual inspection of the “observed vs predicted” plot. Kaplan-Meier plots were overlaid with parametric survival curves to assess the goodness-of-fit during the trial period;
- Long term clinical plausibility of the extrapolations.

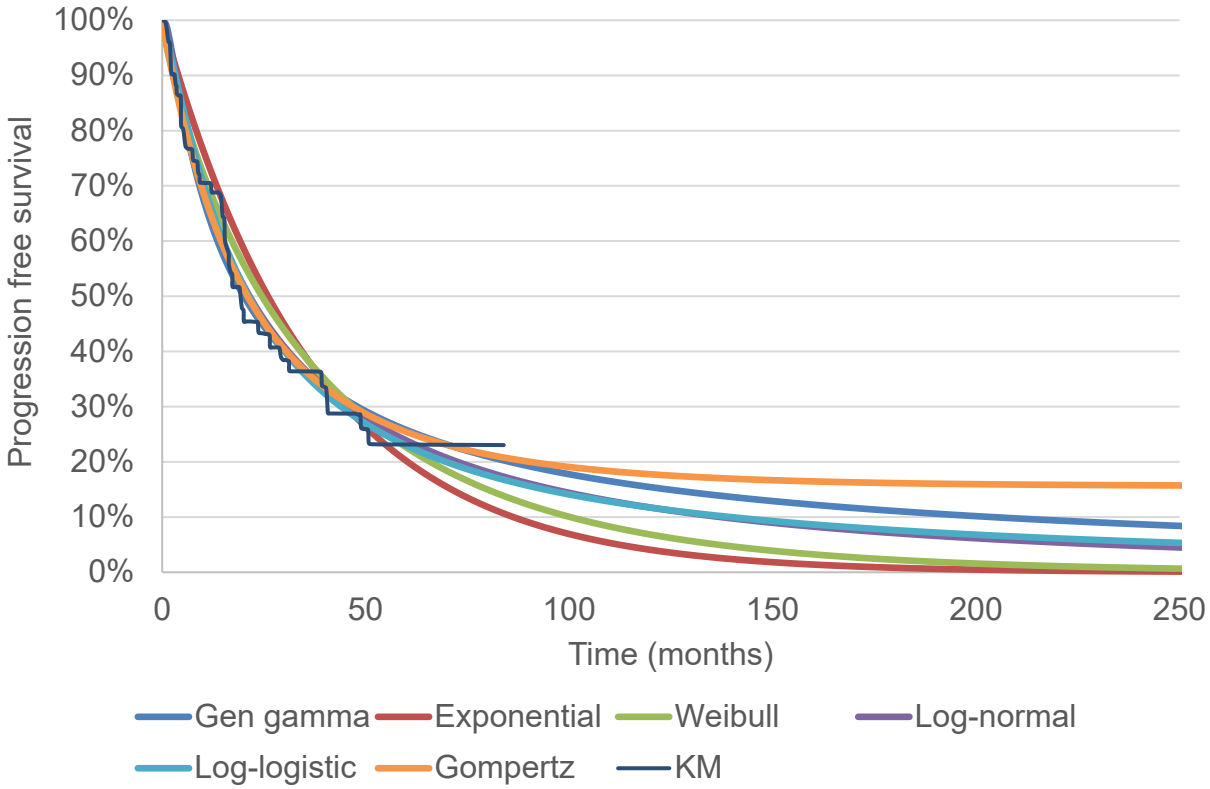
The AIC and BIC for each of the distributions are presented in Table 25, and the parametric distributions fitted to the Kaplan-Meier data is presented in Figure 9.

Table 25. Goodness of fit for parametric distributions fitted to PFS data from PROFILE 1001[23]

Model	AIC	BIC
Exponential	391.772	393.742
Generalised Gamma	381.652	387.563
Gompertz	381.086	385.026
Log-logistic	382.966	386.907
Log normal	381.884	385.824
Weibull	389.420	393.361

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

Figure 9. Parametric models fit to PROFILE 1001 PFS data



All models displayed a good visual fit to the observed data. Gompertz, generalised gamma and log normal had the lowest AIC and BIC values, indicating the best statistical fit. Long term extrapolations were also considered to determine the clinical plausibility of the curves, and an overview of the modelled PFS at key time points for crizotinib by survival extrapolation are presented in Table 26. Although a good statistical fit, the Gompertz curve had the highest estimated mean PFS and a high proportion of patients estimated to be alive after 20 years, suggesting it may be less clinically plausible.

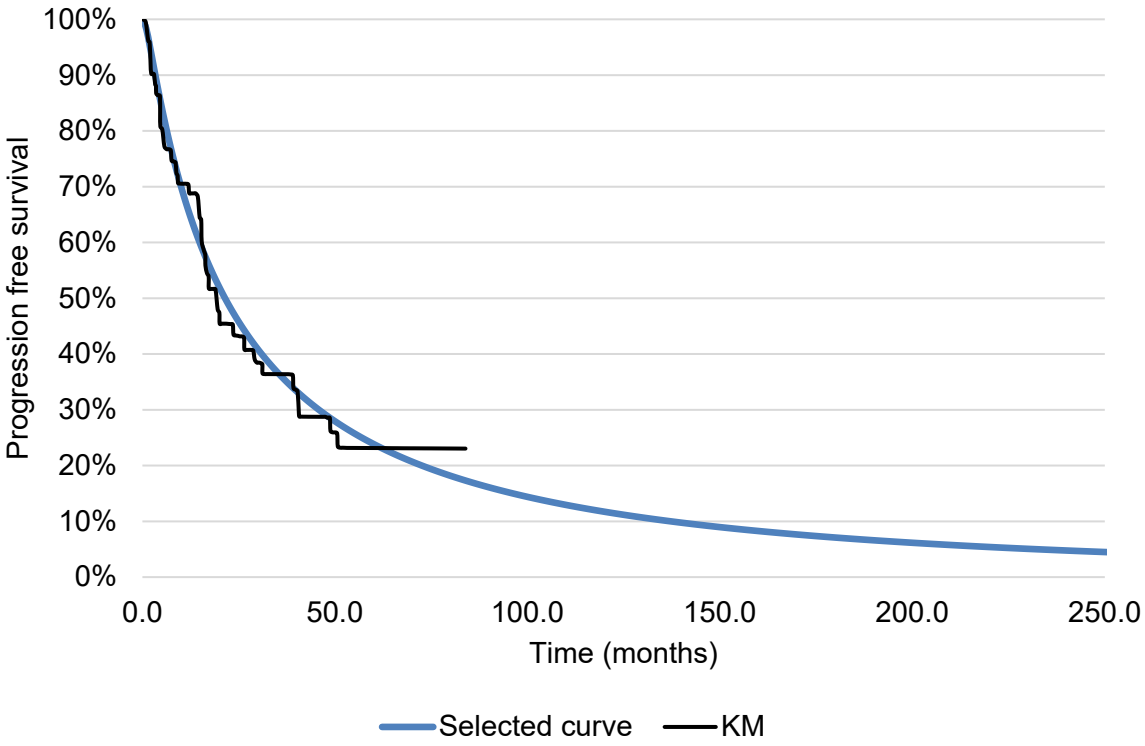
Table 26. Extrapolated PFS figures at key time points

Distribution	Modelled landmarks (PFS)				
	1 year	5 years	10 years	20 years	30 years
	12 months	60 months	120 months	240 months	360 months
Exponential	72.93%	20.10%	4.04%	0.17%	0.01%
Generalised gamma	63.58%	25.74%	15.39%	8.72%	6.10%
Gompertz	65.02%	25.39%	17.74%	15.76%	15.63%
Log-logistic	66.47%	22.91%	11.69%	5.59%	3.55%

Distribution	Modelled landmarks (PFS)				
	1 year	5 years	10 years	20 years	30 years
	12 months	60 months	120 months	240 months	360 months
Log normal	65.96%	23.84%	11.70%	4.78%	2.58%
Weibull	68.89%	22.56%	6.80%	0.79%	0.11%

Taking into consideration the statistical fit, visual fit, and clinical plausibility, the log normal distribution was selected as the preferred base-case distribution (Figure 10). Given the clinical similarity between crizotinib and entrectinib as demonstrated by the STC in Section B.3.12, treatment duration of entrectinib was assumed to be similar to crizotinib and therefore the same PFS curve was applied to both treatment arms (Section B.3.7.2). Consequently, the choice of parametric model has limited impact on the results. Alternative parametric models were explored in scenario analyses to determine the economic impact (Section B.4.4).

Figure 10. Log normal extrapolation for PFS



B.4.2.6.2 Post-progression assumptions

Following disease progression, it is assumed that patients will receive second-line platinum-based chemotherapy with or without atezolizumab plus bevacizumab regardless of the choice of crizotinib or entrectinib as first-line treatment (Figure 1).[17,72] It is further assumed that treatment outcomes will be equivalent. Therefore, post-progression survival has not explicitly been incorporated into this simplified model.

B.4.2.7 Clinical expert validation

Clinical expert opinion highlighted that crizotinib continues to be a sought-after treatment option for patients with ROS1-positive NSCLC. While the comparison of AEs demonstrated that crizotinib and entrectinib were similar (see Section B.3.13), clinicians noted that crizotinib offers distinct advantages over entrectinib in terms of managing certain AEs, specifically weight gain. Clinicians noted that managing weight gain was challenging for them, and while not always rising to a grade 3 or 4 AE, it was an important factor when deciding the optimal treatment for a patient. This is of paramount importance, as minimising the impact of treatment-related side effects is crucial for enhancing patient compliance and overall therapeutic outcomes. The model does not reflect this difference and it could be considered an important uncaptured benefit.

Furthermore, clinician preference and extensive experience with crizotinib have been key factors influencing its utilisation in the treatment of ROS1-positive NSCLC. Given the familiarity and proven efficacy of crizotinib, clinicians have expressed a strong inclination towards its use, which has translated into improved patient outcomes. This preference is grounded in the understanding that crizotinib has consistently demonstrated positive results in the management of ROS1-positive NSCLC, leading to increased confidence among healthcare professionals.

Clinical experts noted that crizotinib should be considered an essential treatment option alongside entrectinib for patients with ROS1-positive NSCLC. The clinical efficacy of crizotinib combined with the preference and experience of clinicians underscores the clinical necessity and relevance of maintaining crizotinib in the therapeutic options for ROS1-positive NSCLC.

B.4.2.8 Uncertainties in the inputs and assumptions

The cost-comparison analysis uses clinical data from single-arm trials in a network to model the incremental cost differences for treating patients with ROS1-positive NSCLC with either crizotinib or entrectinib. Simplifications to the model are based on clinical evidence, expert opinion, and ERG critiques of previous submissions, and reflect the likelihood that survival outcomes of the two treatments will be similar. Uncertainties in the inputs of the cost comparison analysis for crizotinib and entrectinib included the treatment duration (estimated from the modelled PFS extrapolation), time horizon, resource use, AE management, net price of entrectinib and post-progression survival (Table 27). Scenario analyses were conducted to explore the effects of these parameters on the incremental cost (Section B.4.4).

Table 27. Summary of assumptions made for the cost-comparison analysis

Parameter	Assumption
Time horizon	20 years

Parameter	Assumption
Resource use costs	Equivalent for crizotinib and entrectinib
Adverse event management costs	AEs occurring at grade ≥3 in greater than 5% of patients require management, and only in the first cycle
Treatment duration	Equivalent for crizotinib and entrectinib Estimated using a log normal distribution fitted to the latest PROFILE 1001 PFS data
Post-progression treatment	Patients treated with first-line crizotinib or entrectinib will receive the same treatment following progression and experience the same treatment outcomes
Entrectinib drug cost	List price of entrectinib used throughout the analysis, however there is an unknown confidential simple PAS in place.

B.4.3 Base-case results

The total costs over a lifetime horizon are presented for each of the interventions in Table 28. The base-case results show that crizotinib is a less costly alternative to entrectinib when both the list and PAS prices are used, with a total incremental cost reduction of -£23,039.62 and [redacted] respectively.

Table 28. Base-case lifetime cost comparison of crizotinib and entrectinib

Costs	Crizotinib	Entrectinib
Drug acquisition	£230,174.32 (list) [redacted] (PAS)	£253,294.84
Drug administration	£898.86	£898.86
Drug monitoring	£12,262.86	£12,262.86
AE management	£80.90	£0.00
Total	£243,416.93 (list) [redacted] (PAS)	£266,456.55
Incremental		**-£23,039.62 (list)** **[redacted] (PAS)**

B.4.4 Sensitivity and scenario analyses

Since both crizotinib and entrectinib use the same drug monitoring frequency and resource use costs, a change in each of the parameters impacted both treatment arms and thus a one-way sensitivity analysis demonstrated no change to the output of interest (total incremental cost). As such, scenario analyses were conducted to explore alternative assumptions and its impact on the incremental cost. The scenario analyses are detailed in Table 29.

Table 29. Scenarios assessed for cost comparison of crizotinib and entrectinib

Scenario	Base-case	Values assumed for scenario analysis
Chosen extrapolation for PFS	Log normal	Gompertz
		Generalised gamma
		Exponential

Scenario	Base-case	Values assumed for scenario analysis
Resource use	Resource use as described in TA529	ERG preferred resource use (TA529)
Time horizon	20 years	10 years
		30 years
Adverse events	≥5% adverse events	≥2% adverse events

Abbreviations: ERG, evidence review group

B.4.4.1 PFS extrapolation

Three alternative scenarios were performed to investigate the effect of changing the PFS extrapolation approach on the economic analysis. Gompertz and generalised gamma distributions were explored based on sharing the lower AIC and BIC, whilst the exponential distribution was selected due to having the most conservative long term clinical assumptions. Exploring these three scenarios provides the range on uncertainty within this parameter. The results are displayed in Table 30.

The selection of the Gompertz curve produced an incremental cost of -£29,183.04, which was higher than the base case incremental cost. Selecting the generalised gamma curve also increased the total incremental cost to -£26,082.55.

The exponential distribution resulted in an incremental cost of -£18,266.34, which was lower than the base case results.

As described in Section B.4.2.6, crizotinib and entrectinib share the same time on treatment under the clinical equivalence assumption. Therefore, any changes to the PFS assumptions may change the absolute total costs but ultimately the choice of parametric model has limited impact on the results since the selected curve was applied to both treatments.

Table 30. Results of cost comparison analysis using alternative distributions to model PFS

Costs	Crizotinib	Entrectinib
Gompertz distribution		
Drug acquisition	£291,334.68 (list) [redacted]	£320,598.62
Drug administration	£1,089.16	£1,089.16
Drug monitoring	£15,521.26	£15,521.26
AE management	£80.90	£0.00
Total	£308,026.00 [redacted]	£337,209.04
Incremental		**-£29,183.04 (list)** [redacted]
Generalised gamma distribution		
Drug acquisition	£260,467.97 (list) [redacted]	£286,631.42

Company evidence submission: Crizotinib for treating ROS1-positive advanced non-small cell lung cancer.

Costs	Crizotinib	Entrectinib
Drug administration	£993.12	£993.12
Drug monitoring	£13,876.79	£13,876.79
AE management	£80.90	£0.00
Total	£275,418.78 [redacted]	£301,501.33
Incremental		**-£26,082.55 (list)** [redacted]
Exponential distribution		
Drug acquisition	£182,654.43 (list) [redacted]	£201,001.68
Drug administration	£751.00	£751.00
Drug monitoring	£9,731.17	£9,731.17
AE management	£80.90	£0.00
Total	£193,217.50 (list) [redacted]	£211,483.84
Incremental		**-£18,266.34 (list)** [redacted]

B.4.4.2 Resource use

In the TA643 entrectinib appraisal, the ERG disagreed with some of the company's assumptions on disease management resource use and provided alternative monitoring frequencies which were made in consultation with clinical experts to reflect contemporary UK clinical practice.[19] A scenario analysis was conducted to explore the impact on the incremental cost, and the results are displayed in Table 31. When the ERGs preferred resource use assumptions were used in the economic analysis, there was no overall impact on the incremental cost since both entrectinib and crizotinib are assumed to have the same resource use. However, the total monitoring costs for both arms increased to £14,710.36.

Table 31. Results of cost comparison analysis with ERG preferred resource use

Costs	Crizotinib	Entrectinib
Drug acquisition	£230,174.32 (list) [redacted]	£217,723.45
Drug administration	£898.86	£898.86
Drug monitoring	£14,701.36	£14,701.36
AE management	£80.90	£0.00
Total	£245,855.44(list) [redacted]	£268,895.05
Incremental		**-£23,039.62 (list)** [redacted]

B.4.4.3 Time horizon

The time horizon was varied from 20 years (base-case) to 10 years and 30 years. The results are presented in Table 32. With a time horizon of 10 years, the incremental

cost decreased to -£18,762.47. When the time horizon was increased to 30 years, the incremental cost increased to -£25,048.01.

Table 32. Results of cost comparison analysis using alternative time horizons

Costs	Crizotinib	Entrectinib
10 years		
Drug acquisition	£187,593.54 (list) [redacted]	£206,436.90
Drug administration	£766.36	£766.36
Drug monitoring	£9,994.31	£9,994.31
AE management	£80.90	£0.00
Total	£198,435.11 (list) [redacted]	£217,197.58
Incremental		**-£18,762.47** (list) [redacted]
30 years		
Drug acquisition	£250,168.67 (list) [redacted]	£275,297.58
Drug administration	£961.07	£961.07
Drug monitoring	£13,328.08	£13,328.08
AE management	£80.90	£0.00
Total	£264,538.73 [redacted]	£289,586.73
Incremental		**-£25,048.01** (list) [redacted]

B.4.4.4 Adverse events

In the base case analysis, only AEs occurring in at least 5% of patients in the respective clinical trials of crizotinib and entrectinib were included in the analysis. As this captured very few AEs particularly in the entrectinib arm, this was widened to include AEs occurring in at least 2% of patients. This increased the total incremental cost to -£19,785.41 (Table 33). As AE costs are only applied in the first model cycle, the impact to the base-case incremental cost was minimal.

Table 33. Results of cost comparison analysis using management costs for AEs occurring in at least 2% of patients

Costs	Crizotinib	Entrectinib
Drug acquisition	£230,174.32 (list) [redacted]	£253,294.84
Drug administration	£898.86	£898.86
Drug monitoring	£12,262.86	£12,262.86
AE management	£114.48	£26.29
Total	£243,450.51 (list) [redacted]	£266,482.84
Incremental		**-£23,032.33** (list) [redacted]

B.4.5 Subgroup analysis

No subgroup analyses were explored.

B.4.6 Interpretation and conclusions of economic evidence

A cost comparison model was developed for crizotinib versus entrectinib which assumed clinical similarity and considered costs related to drug acquisition and administration, monitoring, and AE management. Overall, at list prices crizotinib had lower costs than entrectinib, with an incremental cost saving of -£23,039.62 ([redacted] with PAS). This was consistently true for the base-case analysis and the various scenarios modelled. The scenario analyses demonstrate that the parameters have very little impact on the overall incremental total costs since these are largely driven by the drug acquisition costs. It is worth noting that the analysis is based on the list price of entrectinib, but there is an unknown confidential PAS in place. However, approximate pricing assessments with an entrectinib PAS estimate considered find crizotinib to remain a cost-neutral treatment option. To conclude, crizotinib exhibits a good use of NHS resources and consistently remains a suitable alternative to entrectinib whilst providing similar health benefits.

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Dear Ross,

Re: ID6289 Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer - Additional Information Request

Thank you for the clarification questions – Pfizer is grateful for the opportunity to submit further evidence for the above appraisal. Responses to the additional requests below. If you do require any further clarification, please do not hesitate to reach out

Your sincerely,

[redacted]
For and on behalf of Pfizer UK

Response to additional information request

1. **Please could you provide an explanation for the difference between the median overall survival for crizotinib in the SACT dataset (21.9 months, 95% CI: 17.7 to 29) compared to the PROFILE 1001 trial (51.4 months, 95% CI: 29.3 to not estimable [NE])?**

The difference in the median overall survival (OS) between the SACT dataset and PROFILE 1001 trial can be explained by the difference in patient characteristics between the two sources of evidence. The inclusion criteria of PROFILE 1001 permitted participants to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with participants with an ECOG PS of 2 only allowed upon agreement between the investigator and sponsor (of which there was only 1 patient).[1] However, patients eligible for crizotinib via the Cancer Drugs Fund (CDF) could have an ECOG PS from 0-2. Additionally, the crizotinib CDF appraisal year four report showed patients with PS 3 also received crizotinib. Therefore patients presenting with a worse health profile have been included in the SACT RWE.[2] Additionally, the PROFILE 1001 trial defined a specific inclusion/exclusion criteria which selected for medically fit patients, whereas the criteria for use of crizotinib in the CDF represented a real world population. This suggests that patients with other comorbidities (and thus a worse health profile) may have also been included in the SACT RWE. In addition, the CNS metastasis rate in both PROFILE 1001 and SACT dataset is not reported and therefore it's not possible to determine if this is a key variable in the outcomes of overall survival.

On average, patients in the SACT RWE dataset were older compared to patients in the PROFILE 1001 trial (median age: 63 years vs. 55 years, respectively), which can determine relative survival rates due to the strong inverse correlation between age and cancer survival.[3,4] The SACT data set also had a larger proportion of patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 compared to the PROFILE 1001 trial (26.4% vs. 1.9%, respectively), showing a higher proportion of patients in the SACT dataset with greater limitations in daily living abilities due to disease severity, wellbeing and more specifically a significantly higher proportion of patients with a greater likelihood of progressing to ECOG grade of 5 (i.e. dead).[1,5]

In addition to the difference in patient characteristics, there were also differences in the median trial follow-up in the SACT dataset which was significantly shorter compared to the PROFILE 1001 trial (17.4 months vs. 62.6 months, respectively), therefore restricting the median progression-free and overall survival for data collected in the RWE dataset.[1,5]

2. **Please could you explain the rationale for calculating time-varying HRs rather than constant HRs for the STC?**

The rationale for calculating time-varying HRs pertains to the proportional hazards assumptions not strictly holding for any of the time to event outcomes. This is can be seen from Figure 5 for progression-free survival (PFS) (CS, Appendix D 2.3.1), Figure 10 for OS (CS, Appendix D 2.3.2) and Figure 15 for Duration of response (DoR) (CS, Appendix D 2.3.5) where the Kaplan-Meier (K-M) curves for crizotinib and Entrectinib are crossing.

3. Please could you provide an additional analysis calculating constant HRs for the STC?

The methodology employed to estimate the constant hazard ratios (HRs) for OS, PFS and DoR, between crizotinib and Entrectinib utilises the Simulated Treatment Comparison (STC) unanchored approach. The method integrates the individual patient data (IPD) from crizotinib trials (PROFILE1001 and OxOnc) with aggregated data (AGD) from Entrectinib trials (ALKA-372-001, STARTRK-1, and STARTRK-2). Initially, the IPD for crizotinib is processed by renaming and transforming variables to ensure comparability, including categorisation of performance status, smoking status, and other relevant factors. For Entrectinib, where only aggregated baseline characteristics and K-M curves are available, pseudo-IPD is generated based on these sources. These datasets are subsequently combined to form a combined dataset, incorporating key covariates for analysis.

This analysis employs the semi-parametric Cox proportional hazards regression model to estimate the effect of crizotinib relative to entrectinib on OS, PFS, and DoR. The model assumes that hazard ratios between groups remain proportional over time, an assumption referred to as proportional hazards.[6] This implies that while the absolute risk may change over time, the ratio of hazards between the groups remains constant.[6]

The Cox model is adjusted for baseline characteristics, with covariates centred at their mean aggregated data values to align patient populations across treatments. Similarly to the time-varying approach, two models were developed: a base case model, which adjusts for age, smoking status, and ECOG performance status, and a sensitivity model, which includes additional covariates such as ethnicity, sex, and histological classification. Entrectinib is set as the reference treatment, and the hazard ratio (HR) for crizotinib is calculated along with 95% confidence intervals to account for uncertainty (see Table 1). The constant HR results follow the same pattern as those obtained from the time-varying approach in terms of direction and magnitude, as there is significant overlap in the 95% confidence intervals of the respective estimates. We believe that this provides supporting evidence that entrectinib and crizotinib have similar clinical effect and supports the cost comparison approach.

Table 1: Summary of Cox Proportional Hazards Model Results and averaged time-varying HR for OS, PFS, and DoR

Outcome	Constant HR [95% CI] Cox Proportional model	Average HR [95% CI] Time-varying approach
OS (base case)	[redacted]	[redacted]
OS (sensitivity)	[redacted]	
PFS (base case)	[redacted]	[redacted]
PFS (sensitivity	[redacted]	
DOR (base case)	[redacted]	[redacted]
DOR (sensitivity)	[redacted]	

CI: confidence interval, DoR: duration of response, HR: hazard ratio, OS: overall survival, PFS: progression-free survival

4. Please could you provide additional analyses where line of treatment and presence of brain metastasis are adjusted for?

Line of therapy

In both the base case and sensitivity models, additional analyses were performed to adjust for prior line of treatment (0, 1, ≥2). The models with this additional adjustment were limited to using individual participant data from the OxOnc trial, as data from the PROFILE 1001trial is not available for this variable. This limitation should be considered when interpreting the results, as the analysis reflects a subset of the patient population in the STC (see Table 2 and Table 3). The results are very similar between the two approaches, in addition to the comparison of results not adjusting for prior line of treatment (Column 'Not adjusted for treatment line (OxOnc trial)') across all three time-to-event outcomes, suggesting that this potential adjustment does not significantly impact the results.

Table 2 Summary of Cox Proportional Hazards Model and averaged time-varying HR results for OS, PFS, and DoR (OxOnc population)

	Additional adjustment on treatment line (OxOnc trial)		Not adjusted for treatment line (OxOnc trial)
+/Outcome	**Constant HR [95% CI] Cox Proportional model**	**Average HR [95% CI] Time-varying approach**	**Average HR [95% CI] Time-varying approach**
OS (base case)	[redacted]	[redacted]	[redacted]
OS (sensitivity)	[redacted]		
PFS (base case)	[redacted]	[redacted]	[redacted]
PFS (sensitivity	[redacted]		
DOR (base case)	[redacted]	[redacted]	[redacted]
DOR (sensitivity)	[redacted]		

Table 3 Summary of logistic regression model results for ORR (OxOnc population)

Outcome	OR [95% CI] Additional adjustment on treatment line	OR [95% CI] No additional adjustment on treatment line
ORR (base case)	[redacted]	[redacted]
ORR (sensitivity)	[redacted]	[redacted]

Brain metastases

Regarding brain metastases, it was not possible to adjust for this variable in either the base case or sensitivity models due to the very small number of patients who presented with brain metastases at baseline (no reported value vs. 18.1%, in the PROFILE 1001 and OxOnc trials, respectively). The limited occurrence of this condition reduces the statistical power to make reliable inferences on its impact within the adjusted models. As such, any potential effects of brain metastases on the outcomes have not been accounted for in these analyses.

References

1. Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol*. 2019;30(7):1121-1126.

2. NHS England. National Cancer Drugs Fund List. Published online August 28, 2024.

3. Cancer Research UK. CRUK average number of deaths per year.xlsx. Published online October 13, 2020. Accessed September 4, 2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/age#heading-Zero

4. Office for National Statistics. Leading causes of death by demographics.xlsx. Published online July 1, 2021.

5. National Disease Registration Service. Crizotinib for treating ROS1-positive advanced non-small cell lung cancer (NSCLC) - data review. Published online 2023.

6. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B Methodol*. 34(2).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID6289_Crizotinib_Summary_Information_Patients_20May24_noCON	Final	No	20 May 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Response: Crizotinib (Xalkori®)

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

Response: Adults with ROS1-positive advanced non-small cell lung cancer (NSCLC).

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

Response: Crizotinib received EU marketing authorisation on 25th August 2016. Crizotinib is indicated for the treatment of adults with ROS1-positive advanced NSCLC.[1] More information is available here: Xalkori | European Medicines Agency (europa.eu)

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

Response:

ALK Positive UK has collaborated with Pfizer on the production of educational materials aimed at patients, such as videos, podcasts, infographics.

Pfizer has also worked with ALK Positive UK through Consultancy/Surveys/Publications to support research into patient preference on drug formulation design, such as types of formulations/dosage forms and routes of administrations preferred by patients.

Pfizer has also provided financial support to the ALK+UK annual conference.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

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

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

Response:

ROS1-positive NCSLC is a type of lung cancer caused by a change in the ROS1 gene. This causes the cancer cells to grow uncontrollably. The ROS1 gene is altered in about 1-2% of lung cancer patients, and generally appears in a particular type of cancer called adenocarcinoma NSCLC. Patients who are ROS1-positive tend to be younger than the average lung cancer patient (50 years in ROS1 NSCLC vs 72 years for all lung cancer types) and have little to no smoking history.[2]

In the UK over 33,000 people are diagnosed with lung cancer each year.[3] Lung cancer is often caught at a late stage (known as advanced cancer), making it difficult to treat. Only about 16% of people survive for five years after diagnosis, and only 9.5% survive to 10 years. This is because most cases are discovered after the cancer has spread to other parts of the body, which makes treatment challenging.[4]

As their cancer progresses, patients report lower quality of life (measured by their: ability to conduct their usual activities, pain, anxiety and depression and self-care abilities). They also report worse physical, emotional and cognitive function, as well as a reduced ability to work. The

treatment for ROS1-positive advanced NCSLC aims to slow the progression of the disease and increase survival.

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

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

Response:

To diagnose a patient with ROS1-positive advanced NCSLC, a small piece of lung tissue is removed through a procedure called a biopsy. Testing is done to the tissue to check if the ROS1 gene change is present [5]. This testing is done through the NHS.

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Crizotinib was the first therapy developed to specifically target the faulty ROS1 protein produced by the altered ROS1 gene responsible for causing ROS1-positive advanced NSCLC. In 2018, crizotinib was reviewed by NICE as a treatment option for patients with ROS1-positive advanced NCSLC.[6] NICE are responsible for evaluating and deciding which treatments should be recommended for use within NHS England (NHSE) based on their clinical benefit and value for money.

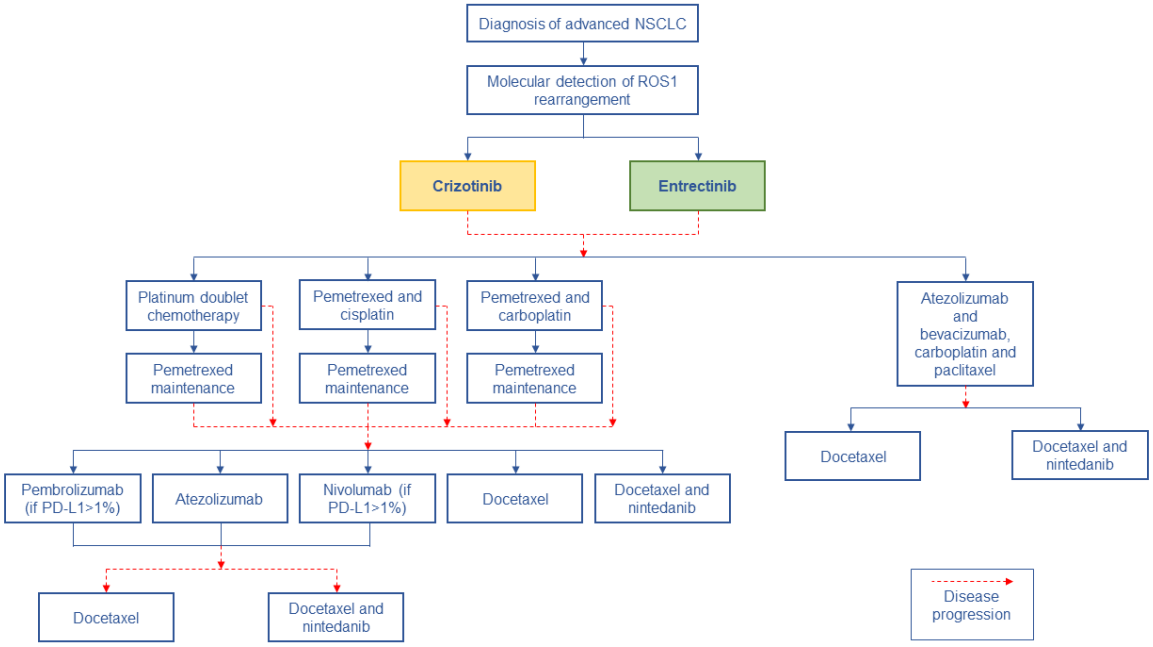
NICE decided to recommend crizotinib for use in the Cancer Drugs Fund (CDF) – a source of funding for cancer drugs in England created in 2016. This meant that the medicine showed promising results in the clinical trial, but not enough evidence was available for NICE to give a full recommendation for use within NHSE at the time. As such, the medicine was recommended for use in the CDF where more time is provided for the company to collect evidence on how well the treatment works in a clinical setting while allowing for it to be accessed by patients. [7]

After the CDF period (5 years), NICE is required to reconsider the new evidence relating to the treatment and make a final recommendation decision. As the CDF period for crizotinib has now come to an end, this is what the current appraisal aims to achieve.

Whilst crizotinib was available via the CDF, another treatment called entrectinib was recommended by NICE in 2020 as a treatment option for patients with ROS1-positive advanced NCSLC.[8] Entrectinib is also a targeted treatment option that works in a similar way to crizotinib.[9]

For adults diagnosed with ROS1-positive advanced NSCLC, NICE management guidance recommends targeted treatment with either crizotinib or entrectinib (Figure 1).[10]

Figure 1: Treatment of ROS1-positive NSCLC. Source: NG122 NICE guidelines



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

Context:

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

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

Response:

Advanced NSCLC is associated with poor survival and also symptoms that negatively impact on patient and caregiver health-related quality of life (HRQoL). A patient survey was conducted in patients with advanced NSCLC across Australia, Belgium, Canada, France, Italy, Turkey, The Netherlands, Sweden, and the United Kingdom. [11]

In order to measure the patients HRQoL, two questionnaires called the EQ-5D and EQ VAS were answered by the patients. The questionnaires assessed mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

The results found that 57% of patients reported having moderate pain or discomfort and 6% reporting to have extreme pain or discomfort. 43% of patients also reported that they experienced moderate anxiety or depression. When it came to the impact on their daily life, 46% of patients reported some difficulties in being able to complete their usual daily activities.

Patients who had a more progressed disease also had a lower HRQoL in comparison to those who were progression free. [11]

The impact on caregivers on needing to provide care to those with advanced NSCLC is also reported. Informal caregivers experience decreased HRQoL, with anxiety/depression problems being reported the most.[12]

The impact of crizotinib on quality of life is discussed further in section 3f of this document.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Crizotinib is an ROS1 inhibitor which works by turning off the faulty ROS1 proteins responsible for uncontrolled cell growth in cancer cells, causing the cancer cells to die.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

Response:

Crizotinib is not required to be used in combination with other medicines.

3c) Administration and dosing

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

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

Response:

Crizotinib is an oral capsule taken twice a day.

3d) Current clinical trials

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

Response:

The key clinical trial investigating crizotinib in ROS1-positive advanced NSCLC is the PROFILE 1001 phase 1 study.[13] The study focused on evaluating the safety, dosing and how well crizotinib works for treating the condition (also known as its efficacy). PROFILE 1001 enrolled 53 patients, all of whom received treatment with crizotinib. Before joining a clinical trial, patients need to give consent and trial doctors need perform medical checks, to confirm if the patients are suitable to join the trial. For PROFILE 1001, to be eligible to participate in the trial patients had to have:

- Confirmed diagnosis of ROS1-positive advanced NCSLC
- Be at least 18 years of age
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (i.e. show they are still able to do some daily activities)
- Their kidneys and liver working correctly
- Disease that can be accurately measured and monitored so it can be tracked during treatment

People could not participate in the trial if they had:

- A recent major surgery, radiation therapy or anticancer therapy
- Active or unstable heart disease
- A prior stem cell transplant
- Were badly affected by their cancer in their ability to carry out daily activities

More information on PROFILE 1001 can be found here[14]: A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer - Full Text View - ClinicalTrials.gov

A scientific paper presenting the results of the most recent data from PROFILE 1001 is available here[13]: Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001 - PubMed (nih.gov)

Since PROFILE 1001, four additional studies (METROS, EUCROSS, AcSé, Oxford Oncology[15-18]) have been published adding to the clinical evidence of crizotinib. All four studies are phase 2 clinical trials exploring the efficacy and safety of crizotinib. While PROFILE 1001 included patients from Australia, South Korea and the USA, METROS, EUCROSS and AcSé included European patients (from Italy, France, German, Spain, Switzerland) and Oxford Oncology (OxOnc) included patients from East Asia.

The OxOnc trial included 127 patients all from China, Japan and Taiwan. Eligible patients for the OxOnc trial were similar to those of PROFILE 1001 in that they had to have a confirmed diagnosis of ROS1-positive advanced NCSLC, be at least 18 years of age, have measurable disease and be well enough to still carry out some daily activities/ participate (ECOG status, 0 to 1). The OxOnc trial is the largest clinical trial exploring crizotinib as a treatment for patients with ROS1-positive advanced NCSLC to date.

More information on OxOnc can be found here[19]: Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC - Full Text View - ClinicalTrials.gov

A scientific paper presenting the results of the most recent data from OxOnc is available here[20]:

Final Overall Survival, Safety, and Quality of Life Results From a Phase 2 Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced NSCLC - PubMed (nih.gov)

All the above mentioned clinical trials were single arm trials, meaning all patients in each trial received the same drug (crizotinib) rather than being split to receive different treatments. As such the trials did not directly compare crizotinib to another drug or placebo. This was because ROS1-positive advanced NSCLC is a rare and advanced disease, so it was more fair and ethical for all the patients to receive treatment with crizotinib.

There is a larger phase 3 clinical trial currently being conducted to directly compare crizotinib against entrectinib as a treatment option for ROS1-positive NSCLC. The trial is still ongoing and more information is available here[21]: Study Details | A Study to Compare the Efficacy and Safety of Entrectinib and Crizotinib in Participants With Advanced or Metastatic ROS1 Non-small Cell Lung Cancer (NSCLC) With and Without Central Nervous System (CNS) Metastases | ClinicalTrials.gov)

3e) Efficacy

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

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

Response:

In PROFILE 1001, most patients (72%) had a response to treatment with crizotinib[13]. The trial also measured the efficacy of crizotinib by determining the overall survival (OS: how long a person lives for) and progression free survival (PFS: how long a person lives until their cancer gets worse). In PROFILE 1001, patients receiving crizotinib had a median overall survival of 51.4 months, and median progression free survival was 19.3 months[13]. In the OxOnc trial, the median overall survival was 44.2 months, and the progression free survival was last reported as 15.9 months[20].

As well as evidence from clinical trials, there is also evidence that can be taken from patients who have received crizotinib outside of a clinical trial setting, under the care of their doctors. As crizotinib was available for patients as a treatment option via the CDF for 5 years, roughly 30 patients each year were able to receive treatment. Additionally, crizotinib is also available as a routine treatment option in other countries outside of the UK. As such, there is a large amount of evidence relating to its use, known as real world evidence (RWE). Overall, the effectiveness outcomes from RWE were found to be consistent with clinical trial data and support the use of crizotinib in patients with ROS1-positive NSCLC. RWE also showed that crizotinib is a key treatment option that clinicians rely on and consistently prescribe to their patients. [22-26]

Since crizotinib and entrectinib are the recommended treatment options for ROS1-positive advanced NCSLC, it is important to understand how crizotinib compares to entrectinib. As the key clinical trials for crizotinib (PROFILE 1001 and OxOnc) were both single arm trials and did not directly compare crizotinib to entrectinib, a statistical method was used to indirectly compare the two treatment options to determine how their efficacy and safety compare. The statistical method is known as an indirect treatment comparison (ITC). The results of the ITC showed that crizotinib and entrectinib have similar efficacy in progression free survival and overall survival. This evidence demonstrates that the relative treatment effects of crizotinib and entrectinib are comparable, suggesting they both delay disease progression and extend survival to the same degree.

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

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

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

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

Response:

In addition to assessing efficacy and safety, the OxOnc and EUCROSS trials captured the impact of crizotinib on a patient's health-related quality of life (HRQoL). [16, 20, 27] This was assessed during the trial by getting patients to complete two questionnaires: 1) the EORT QLQ C-30, which evaluates quality of life in cancer, and 2) the EORTC QLQ LC-13 which evaluates quality of life in lung cancer specifically[28].

The EORT QLQ C-30 questionnaire is used to assess the following elements:

- function (physical, role, cognitive, emotional, and social)
- symptoms (fatigue, pain, and nausea and vomiting)
- a global health status/quality of life scale (global QoL)
- additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea).

In the OxOnc trial, patients receiving crizotinib had a marked improvement in global QoL compared to how they were at the start of the clinical trial before treatment (baseline). By cycle 60 of treatment, more than half of the patients on treatment were noted to have improved or stable scores in their function. Improvements were also seen in symptoms, with the highest improvement seen in appetite loss, fatigue, dyspnoea, insomnia, and pain[20].

Similarly, in the EUCROSS trial, patients receiving crizotinib also had an improvement in global QoL from baseline. Steady improvements were also seen in the other elements of the QLQ C-30 relating to function, and an improvement in symptoms such as coughing, dyspnoea and chest pain in the QLQ LC-13[16].

Advanced NSCLC is associated with poor survival and symptoms that negatively impact patients' and caregivers' health-related quality of life. Data suggests that treatment with crizotinib

substantially improved or maintained quality of life for people with ROS1-positive advanced NSCLC compared to no treatment.

3g) Safety of the medicine and side effects

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

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

Response:

During all clinical trials, the safety of the treatments are monitored by recording any unexpected medical problems trial participants experience. These are known as adverse events (AEs), which may or may not be related to the treatment the participant is receiving.

Almost all patients receiving crizotinib in the clinical trials experienced some form of an adverse event, however most of the adverse events were grade 1 or 2 (considered less severe). In the EUCROSS trial 12.5% of patients experienced what would be defined as a serious adverse event (SAE), and in METROS this was 14.7% of trial patients.[15, 16] Across all crizotinib trials that reported AE data (EUCROSS, METROS, OxOnc, and PROFILE 1001) the most frequently reported treatment-related AEs were vision disorders (ranging from 23–87% of patients), tiredness (12–58%), and stomach-related AEs such as vomiting (27–38%), nausea (40–51%), diarrhoea (27–56%), and constipation (15–34%). [13, 15, 16, 20]

In the OxOnc trial, 17.3% of patients had to reduce their dose of crizotinib due to their adverse events, and 2.4% of patients had to stop treatment completely.

Overall, the results of the trials suggest that the side effects associated with crizotinib treatment are manageable and crizotinib is well tolerated.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Response:

Crizotinib is a targeted treatment option for patients with ROS-positive advanced NSCLC which works to turning off the faulty ROS1 proteins in cancer cells, causing the cancer cells to die. In 2018 it was recommended for use via the CDF, and has been a consistently used treatment option for patients despite the introduction of entrectinib. Findings from RWE collected from patients who have received crizotinib are in line with those of the clinical trials and support the use of

crizotinib in patients with ROS1-positive NSCLC for delaying disease progression and extending survival. [22-26]

HRQoL data also shows that treatment with crizotinib substantially improved or maintained quality of life for people with ROS1-positive advanced NSCLC compared to no treatment.[16, 20, 27] When compared to another key treatment, entrectinib, the results of the ITC showed that crizotinib and entrectinib have similar efficacy in delaying disease progression and extending survival.

Overall, the evidence shows that crizotinib is a key treatment option for patients with ROS1-positive advanced NSCLC alongside entrectinib.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

Response:

As with all medicines, patients can experience side effects with crizotinib treatment, however, in the clinical trials the side effects were manageable.[13, 20] Therefore, the company does not consider that crizotinib has disadvantages compared to entrectinib received by patients with ROS1-positive NSCLC.

3i) Value and economic considerations

Introduction for patients:

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

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

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

Response:

The bullets below give a suggestion of structure, subheadings and key points to give the context of how the cost effectiveness of the treatment has been modelled. Addressing each of the bulleted points below should be kept to a few sentences.

How the model reflects the condition

- What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

Modelling how much a treatment extends life

- Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).
- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.
- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?
- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?
- Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?
- Are there any data you have presented to support your modelled outcomes being plausible?

Cost effectiveness results

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Additional factors

- Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented
- Are there any benefits or disadvantages of the treatment not captured in the modelling?

Response:

How the model reflects ROS1-positive NSCLC

An economic model was created to help assess the value of crizotinib to the NHS. The model estimated the total costs of treating a patient with crizotinib across their lifetime. Since the average age of patients in the PROFILE 1001 trial was 55 years, the chosen time horizon was 20

years, as this was considered long enough to cover a patient with ROS1-positive advanced NCSLC average lifetime. [13]

As mentioned, the two recommended targeted treatment options for patients with ROS1-positive NSCLC are crizotinib and entrectinib. As such, the model aimed to compare the cost of managing a patient with crizotinib against the cost of managing a patient with entrectinib. Since the ITC demonstrated clinical similarity between the two treatments, clinical efficacy was assumed to be the same, and the model focussed on the difference between the two treatments in terms of cost.

Modelling costs

The costs included in the economic model were:

- Drug treatment costs: the total costs of treatment with crizotinib and entrectinib.
- Drug administration costs: the cost of helping a patient take crizotinib and entrectinib. As they are cancer drugs, they are taken by patients in hospital under the care of medical professionals. For both treatments these were the same as they are both oral drugs taken in the same manner/ clinical settings.
- Drug monitoring costs: the costs associated with monitoring patients on treatment, such as blood tests, GP visits, cancer nurse visits, X-rays and scans. Both crizotinib and entrectinib require the same type and amount of monitoring, so these costs were the same in the model. Drug monitoring costs were applied in the model for the amount of time patients were on treatment.
- AE costs: the adverse events considered more severe (grade 3 and 4) reported in the respective key clinical trials for crizotinib and entrectinib were included in the economic model. Only AEs which affected at least 5% of patients were included. For crizotinib, these were hypophosphatemia and neutropenia, and for entrectinib this was weight gain. The costs associated with managing these adverse events were included in the model. [13, 29]

Modelling how much crizotinib extends life

PFS (the amount of time before a patient experiences a worsening in their disease) was used to estimate the amount of time patients are on treatment, since crizotinib and entrectinib are advised to be given until disease progression occurs.[1, 9] As the ITC was able to demonstrate that PFS of crizotinib and entrectinib are similar, the same duration of treatment was used for both treatments. The model needs to measure the costs over a patient lifetime, however clinical trials are only typically conducted for a few years. Therefore, the PFS from PROFILE 1001 had to be extrapolated to estimate the total treatment duration over the full time horizon.

Cost-savings results

All of the costs were totalled across the time horizon for each treatment and then compared, and the difference in total costs was calculated. The model found that treatment with crizotinib provided cost savings in comparison to entrectinib.

Uncertainty

The model is associated with some uncertainty. Firstly, to estimate the long-term total costs, extrapolation methods were used. As such there is uncertainty in how accurately the extrapolations reflect reality. Secondly, it was assumed that the clinical effectiveness of crizotinib and entrectinib are the same based on the results of the ITC. From the ITC we were able to conclude that there is no statistical difference in efficacy between crizotinib and entrectinib. However, as they were not directly compared in a clinical trial, there is some uncertainty relating to this estimation method. Whilst there were limitations to the ITC method used, it was considered the best available approach for estimating the comparative effectiveness between these treatment options based on the available evidence. Other estimation methods were explored to confirm that the ITC approach used was the most appropriate approach.

Additional Information

As the economic model focuses on the associated costs of managing patients on crizotinib compared to entrectinib, it does not capture any other wider benefits crizotinib provides, for example impact on quality of life.

3j) Innovation

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

Response:

Crizotinib was the first available targeted treatment option for patents with ROS1-positive advanced NCSLC, and has since remained a key treatment chosen by clinicians to treat their patients. [1]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Since ROS1 testing is routinely done in the NHS, all eligible patients can be diagnosed with ROS1-positive advanced NCSLC and access targeted treatment with crizotinib. As such there are no expected equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

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

Response:

- European Medicine's Agency - EPAR Summary for the Public for crizotinib: Xalkori; INN-crizotinib (europa.eu)
- Electronic Medicines Compendium – Summary of Product Characteristics for crizotinib: http://www.medicines.org.uk/emc/medicine/27168

- Crizotinib original NICE appraisal (TA529): Overview | Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer | Guidance | NICE
- Entrectinib NICE appraisal (TA643): https://www.nice.org.uk/guidance/ta643
- PROFILE 1001 Results - Shaw et al. 2019: Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001 - ScienceDirect
- OxOnc Results – Wu et al. 2022: Final Overall Survival, Safety, and Quality of Life Results From a Phase 2 Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced NSCLC - PubMed (nih.gov)
- METROS – Landi et al. 2019: Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial - PubMed (nih.gov)
- AcSe: Moro-Siblot et al. 2019: Crizotinib in c-MET- or ROS1-positive NSCLC: results of the AcSé phase II trial - PubMed (nih.gov)
- EUCROSS – Michels et al. 2019: Safety and Efficacy of Crizotinib in Patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer (EUCROSS): A European Phase II Clinical Trial - PubMed (nih.gov)
- Patient advocacy group: About The ROS1ders | The ROS1ders
- Patient advocacy group: Home | ALK Positive UK | Supporting patients of ALK+ lung cancer

Further information on NICE and the role of patients:

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

4b) Glossary of terms

Response:

ROS1-positive	Describes a type of cancer in which cells have a change in structure in the ROS1 gene or make too much ROS1 protein
EORTC QLQ-C30	A questionnaire to measure quality of life, specific to cancer
EQ-5D-5L	A questionnaire to measure quality of life
Global QoL	An overall score to reflect how patients feel overall about their health and quality of life
Progression-free survival	The length of time that a patient lives with a disease without it getting worse
Overall survival	The length of time that a patient lives before dying
HRQoL	The impact of someone's health on their quality of life

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. European Medicines A. Xalkori: EPAR - Product Information: Summary of Product Characteristics. 2021 2021/07/16/.
2. Eldridge L. What Is ROS1-Positive Lung Cancer? 2024 [updated February 2024. Available from: https://www.verywellhealth.com/ros1-positive-lung-cancer-2248947.
3. National Lung Cancer Audit annual report. Royal College of Physicians; 2022 2022/01//.
4. Cancer Research UK - Lung cancer statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Two.
5. Bubendorf L, Büttner R, Al-Dayel F, Dietel M, Elmberger G, Kerr K, et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. Virchows Arch. 2016;469(5):489-503.
6. National Institute for H, Care E. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer. 2018 2018.
7. National Institute for H, Care E. Cancer Drugs Fund Managed Access Agreement: Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer. 2018 2018.
8. National Institute for H, Care E. TA643: Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer. 2020 2020.
9. European Medicines A. Rozlytrek: EPAR - Product Information: Summary of Product Characteristics. 2020 2020/09/11/.
10. National Institute for H, Care E. NG122: Lung cancer: The diagnosis and treatment of lung cancer: Treatment. 2019 2019.
11. Chouaid C, Agulnik J, Goker E, Herder GJM, Lester JF, Vansteenkiste J, et al. Health-Related Quality of Life and Utility in Patients with Advanced Non–Small-Cell Lung Cancer: A Prospective Cross-Sectional Patient Survey in a Real-World Setting. Journal of Thoracic Oncology. 2013;8(8):997-1003.
12. Yang Y, Liu L, Chen J, Gan Y, Su C, Zhang H, et al. Does caring for patients with advanced non-small cell lung cancer affect health-related quality of life of caregivers? A multicenter, cross-sectional study. BMC Public Health. 2024;24(1):224.

13. Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2019;30(7):1121-6.
14. ClinicalTrials.gov - A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001) [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00585195.
15. Landi L, Chiari R, Tiseo M, D'Incà F, Dazzi C, Chella A, et al. Crizotinib in MET-Deregulated or ROS1-Rearranged Pretreated Non-Small Cell Lung Cancer (METROS): A Phase II, Prospective, Multicenter, Two-Arms Trial. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research. 2019;25(24):7312-9.
16. Michels S, Massutí B, Schildhaus H-U, Franklin J, Sebastian M, Felip E, et al. Safety and Efficacy of Crizotinib in Patients With Advanced or Metastatic ROS1-Rearranged Lung Cancer (EUCROSS): A European Phase II Clinical Trial. J Thorac Oncol. 2019;14(7):1266-76.
17. Wu Y-L, Yang JC-H, Kim D-W, Lu S, Zhou J, Seto T, et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(14):1405-11.
18. Moro-Sibilot D, Cozic N, Pérol M, Mazières J, Otto J, Souquet PJ, et al. Crizotinib in c-MET- or ROS1-positive NSCLC: results of the AcSé phase II trial. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2019;30(12):1985-91.
19. ClinicalTrials.gov - Phase II Safety and Efficacy Study of Crizotinib in East Asian Patients With ROS1 Positive, ALK Negative Advanced NSCLC [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01945021.
20. Wu Y-L, Lu S, Yang JC-H, Zhou J, Seto T, Ahn M-J, et al. Final Overall Survival, Safety, and Quality of Life Results From a Phase 2 Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced NSCLC. JTO Clin Res Rep. 2022;3(10):100406.
21. ClinicalTrials.gov - A Study to Compare the Efficacy and Safety of Entrectinib and Crizotinib in Participants With Advanced or Metastatic ROS1 Non-small Cell Lung Cancer (NSCLC) With and Without Central Nervous System (CNS) Metastases [Available from: https://clinicaltrials.gov/study/NCT04603807.
22. Waterhouse D, Iadeluca L, Sura S, Wilner K, Emir B, Krulewicz S, et al. Real-world outcomes among crizotinib-treated patients with ROS1-positive advanced non-small-cell lung cancer: a community oncology-based observational study. Target Oncol. 2022;17(1):25-33.
23. Zhang Y, Zhang X, Zhang R, Xu Q, Yang H, Lizaso A, et al. Clinical and molecular factors that impact the efficacy of first-line crizotinib in ROS1-rearranged non-small-cell lung cancer: a large multicenter retrospective study. BMC Med. 2021;19(1):206.
24. Xu H, Zhang Q, Liang L, Li J, Liu Z, Li W, et al. Crizotinib vs platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer with different ROS1 fusion variants. Cancer Medicine. 2020;9(10):3328-36.
25. Zheng J, Cao H, Li Y, Rao C, Zhang T, Luo J, et al. Effectiveness and prognostic factors of first-line crizotinib treatment in patients with ROS1-rearranged non-small cell lung cancer: A multicenter retrospective study. Lung Cancer. 2020;147:130-6.
26. Vuong HG, Nguyen TQ, Nguyen HC, Nguyen PT, Ho ATN, Hassell L. Efficacy and safety of crizotinib in the treatment of advanced non-small-cell lung cancer with ROS1 rearrangement or MET alteration: a systematic review and meta-analysis. Target Oncol. 2020;15(5):589-98.
27. Michels S, Gardizi M, Schmalz P, Thurat M, Pereira E, Sebastian M, et al. MA07.05 EUCROSS: A European Phase II Trial of Crizotinib in Advanced Adenocarcinoma of the Lung Harboring ROS1 Rearrangements - Preliminary Results. Journal of Thoracic Oncology. 2017;12(1):S379-S80.
28. EORTC Quality of Life -Questionnaires and tools [Available from: https://qol.eortc.org/questionnaires/.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Clarification questions

June 2024

File name	Version	Contains confidential information	Date
ID6289_Crizotinib_EAG_Clarification_Letter_Response_25June24_noCON_redacted.docx	1.0	No	25 June 2024

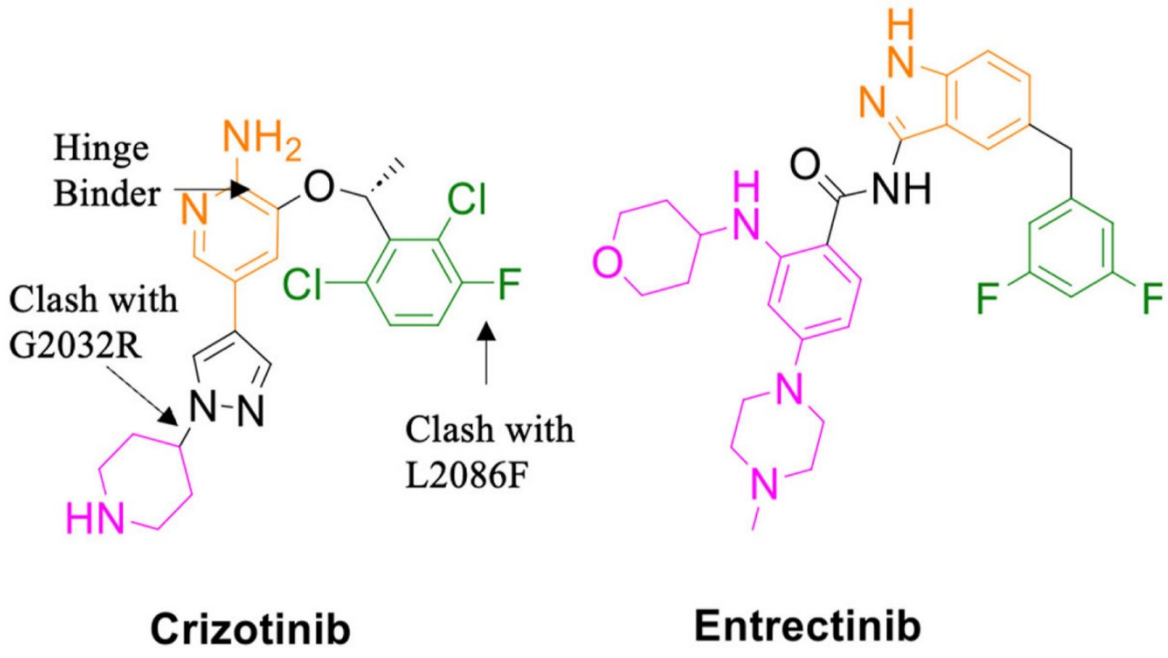
Section A: Clarification on effectiveness data

Clinical effectiveness

A1. Priority question. Please provide information about the similarities and differences between crizotinib and entrectinib in terms of their <u>pharmacokinetic properties and mechanisms of action.</u> Where differences are identified, please justify why these differences do not affect patient outcomes.

Crizotinib and entrectinib are both small molecule tyrosine kinase inhibitors (TKI) that target specific genetic alterations in cancer cells. Crizotinib was the first approved targeted agent for ROS1 receiving European approval in 2016.[1] Entrectinib received conditional marketing authorisation in 2020.[2] They share a similar mechanism of action and differ in their pharmacokinetic properties.

Figure 1. Chemical structure of crizotinib and entrectinib



Source: Ou et al. (2024) [3]

Mechanism of Action

Crizotinib is a potent inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and c-MET. By binding to the ATP-binding site of these kinases, crizotinib prevents their activation and downstream signalling, thereby inhibiting tumour growth and survival.

Entrectinib also inhibits ALK, ROS1, and c-MET, but it additionally targets TRK receptors. Similar to crizotinib, entrectinib blocks the activation of these kinases, leading to the disruption of signalling pathways involved in cancer cell proliferation and survival.

Pharmacology

Small molecule kinase inhibitors are traditionally classified into five types (type I–V) depending on their mode of action. Currently, all ROS1 TKIs are either type I or II inhibitors. Briefly, type I inhibitors bind reversibly primarily to the active kinase domain and type II inhibitors bind to the inactive kinase domain that sometimes extends to the back pocket.[3] Crizotinib and entrectinib are both type 1 non-cyclic compounds.

Pharmacokinetic properties

Crizotinib is extensively metabolized in the liver, primarily via the cytochrome P450 enzyme CYP3A4/5. It has a relatively long elimination half-life of approximately 42 hours. Crizotinib is mainly eliminated through faeces (63%) and to a lesser extent through urine (22%).

Entrectinib is also predominantly metabolized by pre CYP3A4 (it's major active metabolite is M5) and this is highly bound to human plasma proteins independent of drug concentrations. The elimination half-lives of entrectinib and M5 were estimated to be 20 hours and 40 hours, respectively. Entrectinib is eliminated through both faeces (84%) and urine (11%). In terms of absorption, neither drug has a clinically significant effect of food on absorption.

Crizotinib is administered once daily and entrectinib is administered twice daily, ensuring sustained therapeutic levels throughout the dosing interval.

Crizotinib and entrectinib are metabolized by similar liver enzymes, including CYP3A4. Interindividual variability in the activity of these enzymes can lead to differences in drug metabolism and potential drug-drug interactions. However, dose adjustments can be made based on individual patient characteristics or concomitant medications to account for these variations and minimize any potential impact on

patient outcomes. crizotinib is administered orally as a twice daily dose whereas entrectinib is administered orally as a once daily dose.

Both drugs effectively inhibit the same target kinases involved in cancer cell growth with the exception of entrectinib additionally targeting TRK receptors. Overall, crizotinib and entrectinib are considered clinically similar.

A2. Priority question. Please undertake formal statistical testing to support the claim that crizotinib and entrectinib are similar in terms of efficacy and safety.

Evidence presented as part of the clinical effectiveness systematic literature review (SLR) (Sections B.3.1 to 3.8, Appendix D.1, D.3, E, F) for crizotinib and entrectinib involved a qualitative comparative summary of the study results, prior to the population adjustment indirect comparison with respect to study design, patient baseline characteristics, and outcomes. The study populations were deemed clinically similar, and thus an indirect treatment comparison (ITC) by means of a simulated treatment comparison (STC) was conducted to quantify the relative effectiveness of crizotinib vs entrectinib. The results for progression-free survival (PFS), duration of response (DOR) and overall/objective response rate (ORR) found no statistically significant differences between crizotinib and entrectinib, though there was a consistent trend in the results being in favour of crizotinib. There was also no statistically significant difference in overall survival (OS) with crizotinib compared with entrectinib. Overall, the main findings of the ITC suggest comparable efficacy profiles between the two treatments: the 95% confidence intervals for the hazard ratios (HR) cross 1, and as such the null hypothesis of no difference cannot be rejected by the evidence.

In addition, per request we conducted further formal tests for both efficacy and safety/tolerability outcomes, where data were available. For OS and PFS, the log-rank test between crizotinib (pooled raw data from PROFILE 1001 and OxOnc) and entrectinib (pooled raw data from ALKA-372-001, STARTRK-1 and STARTRK-2) was performed. This non-parametric test compares the survival distributions between the two treatment groups with a null hypothesis of no difference in survival probabilities. For both outcomes, the p-values were higher than 5%, and therefore there are no statistically significant differences in the survival distributions between

the 2 treatments (see Table 1). The same conclusion can be drawn from calculating the unadjusted HR based on the same data, where for both outcomes, the value of null effect (HR=1) is included in the 95% confidence interval.

Table 1. Results of Log-rank test on OS and PFS of raw data of crizotinib and entrectinib

Outcome	p-value from log-rank test	Unadjusted HR of crizotinib vs entrectinib [95% CI]
OS	0.4	[redacted]
PFS	0.3	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival

Regarding ORR, we conducted a two-proportion z-test with a null hypothesis assuming that the observed proportions are equal between the two treatments. The same test was applied to any grade treatment-related adverse events (TRAE) and treatment discontinuation, which were the only outcomes for which input data were available for both treatments. For all outcomes, the p-values were higher than 5% and therefore no statistically significant difference in proportions between the two treatments (Table 2).

Table 2 Results from two-proportion z-test on efficacy and safety/tolerability outcomes

Outcome	Input studies	Proportion in crizotinib	Proportion in Entrectinib	p-value
ORR	Crizotinib (PROFILE 1001, Shaw 2019[4]) Entrectinib (Drilon 2022[5])	[redacted]	[redacted]	0.574
	Crizotinib (OxOnc, Wu 2018[6]) Entrectinib (Drilon 2022[5])	[redacted]	[redacted]	0.483
Any grade TRAE	Crizotinib (OxOnc, Wu 2018[6]) Entrectinib (Dziadzjuszko 2021[7])	[redacted]	[redacted]	0.08
Treatment discontinuation	Crizotinib (PROFILE 1001, Shaw 2014[8]) Entrectinib (Drilon 2022[5])	[redacted]	[redacted]	0.35
	Crizotinib (OxOnc, Wu 2022[9]) Entrectinib (Drilon 2022[5])	[redacted]	[redacted]	0.23

Abbreviations: ORR: objective response rate; OxOnc: Oxford Oncology; TRAE: treatment-related adverse event

We explored conducting non-inferiority tests, however determining the non-inferiority margin (NIFm) in ROS1-positive population is challenging given the lack of non-inferiority trials in this specific population, and thus using NIFm from the broader

NSCLC population might not be representative. In addition, considering that the 95% confidence interval from the STC is wide, given the unanchored and indirect nature of the comparison, contrasting the upper limit with existing NIFms does not appear to be a reasonable testing process to gauge non-inferiority. Furthermore, there was limited time within the clarification period to be able to conduct the analysis. Finally, we noted that demonstrating non-inferiority is not a stipulation for a cost-comparison appraisal. The aim is to demonstrate *clinical similarity*, and where there is a lack of head-to-head data, the use of an ITC/network meta-analysis (NMA) in a cost-comparison appraisal has been accepted by NICE, with similarly uncertain results considered adequate to demonstrate similar efficacy across treatments (for example TA836, TA925).[10,11] Therefore, given the time constraints within the clarification period, a non-inferiority test has not been conducted.

A3. Priority question. Current NICE guidelines recommend crizotinib as a first-line therapy. Clinical effectiveness data presented in the CS have been collected from patients who were treated with crizotinib in the first-line, second-line and later-line settings. Please provide evidence that line of treatment does not have an impact on the clinical effectiveness of crizotinib.

The relationship between the clinical effectiveness of crizotinib for ROS1-positive NSCLC treatment and the treatment line in which crizotinib was administered, has been reported in two clinical trials and three retrospective studies. Collectively, these studies found no evidence that crizotinib was less efficacious in pretreated patients compared to those receiving crizotinib in the first line.

In the OxOnc trial, no differences in ORR were found, and while numerical differences were noted in OS, the confidence intervals were overlapping.[6,9] In the EUCROSS trial, no differences in ORR, DCR, PFS, and OS were detected between groups who had received 0, 1, or 2 treatment lines prior to crizotinib initiation.[12]

Three retrospective studies that assessed survival differences for ROS1-positive NSCLC patients (n=23-36) as a function of crizotinib treatment line (1, 2, or ≥3 prior lines of treatment) were conducted in China.[13–15] Li et al. (2018) found no significant differences in PFS or OS for first-line vs second-line and first-line vs later-line administration of crizotinib using univariable analyses.[13] Liu et al. (2019) reported no significant differences in RRs or median PFS for patients treated with crizotinib in the

first-line compared to later lines.[14] Finally, using single- and multi-variate analyses, Zhu et al. (2019) did not find differences in median PFS based on treatment line.[15]

A4. Priority question. Please provide OS, PFS, DOR and ORR (OxOnc trial only) subgroup analysis results by prior lines of treatment for advanced NSCLC (i.e., previously untreated versus ≥1 prior lines of treatment) from the PROFILE 1001 and OxOnc trials.

Table 3 and Table 4 below present the results available for both OxOnc (data cut-off: July 2020) and PROFILE 1001, considering subgroups based on number of prior lines of treatment. Results stratified by prior regimens were not available in PROFILE 1001 for the DOR outcome. Patients with at least one prior regimen represented majority of patients included in OxOnc, with only 24 untreated patients included. Patients without any prior regimen seemed to have a better PFS, OS, DOR and higher chance of achieving response, although conclusions are limited given the low sample size. Similar findings were observed in PROFILE 1001, but conclusions were limited given low sample sizes and immature data.

Table 3. Subgroup analyses in OxOnc (data cut-off: July 2020) based on prior regimens

Outcome		Untreated patients	At least 1 prior regimen
PFS (by KM estimates)	Sample size	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	Median PFS [95% CI]	[redacted]	[redacted]
OS (by KM estimates)	Sample size	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	Median OS [95% CI]	[redacted]	[redacted]
DOR (by KM estimates)	Sample size	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	Median DOR [95% CI]	[redacted]	[redacted]
ORR (CR+PR)	Sample size	[redacted]	[redacted]
	Number of events	[redacted]	[redacted]
	ORR% [95% CI]*	[redacted]	[redacted]

*CI based on exact binomial method

Abbreviations: CI: confidence interval; CR: complete response; DOR: duration of response; KM: Kaplan-Meier; NA: not applicable; ORR: objective response rate, OS: overall survival; PFS: progression-free survival; PR: partial response

Table 4. Subgroup analyses in PROFILE 1001 based on prior regimens

Outcome		Untreated patients	At least 1 prior regimen
PFS (by KM estimates) ***DCO: November 2014***	Sample size		
	Number of events		
	Median PFS [95% CI]		
OS (by KM estimates) ***DCO: November 2014***	Sample size		
	Number of events		
	Median OS [95% CI]		
ORR (CR+PR) ***DCO: June 2018***	Sample size		
	Number of events		
	ORR% [95% CI]*		

*CI based on exact binomial method

Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; KM: Kaplan-Meier; NA: not applicable; ORR: objective response rate, OS: overall survival; PFS: progression-free survival; PR: partial response

A5. Priority question. Please provide OxOnc trial OS and DOR subgroup analysis results stratified by presence of brain metastases at baseline.

When considering patients with brain metastases at baseline within OxOnc, the following results were obtained for PFS, OS, DOR and ORR (see Table 5). Patients without brain metastases at baseline seemed to have a better PFS, OS, DOR and higher chance of achieving response. We would express extreme caution in attempting to interpret these findings or in drawing any conclusions given the low sample size of patients with brain metastasis at baseline.

Table 5. Subgroup analyses in OxOnc based on presence of brain metastases at baseline

Outcome		No brain metastases	Brain metastases*
PFS (by KM estimates)	Sample size		
	Number of events		
	Median PFS [95% CI]		
OS (by KM estimates)	Sample size		
	Number of events		
	Median OS [95% CI]		
DOR (by KM estimates)	Sample size		
	Number of events		
	Median DOR [95% CI]		
ORR (CR+PR)	Sample size		
	Number of events		
	ORR% [95% CI]**		

*Based on CRF. 23 patients were considered as having brain metastases based on IRR assessment (% ORR [9R% CI]: 73.9 [51.6, 89.8] with vs 70.0 [55.4, 82.1] without; Median PFS [95% CI]: 10.2 [5.6, 13.1] with vs 18.8

[13.1, NR] without).
** CI based on exact binomial method
Abbreviations: CI: confidence interval; CR: complete response; KM: Kaplan-Meier; NA: not applicable; ORR: objective response rate, OS: overall survival; PFS: progression-free survival; PR: partial response

A6. Please provide (using reverse Kaplan-Meier methodology):

- **the PROFILE 1001 trial PFS median follow-up from the July 2018 data cut-off**
- **the OxOnc trial, PFS median follow-up from the June 2020 data cut-off.**

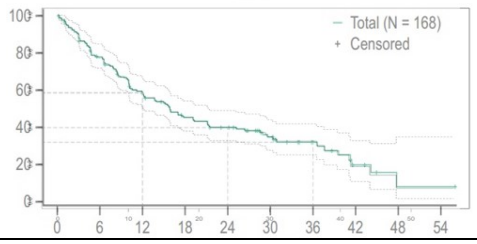
Using the reverse Kaplan-Meier methodology on R, a median PFS follow-up of 59.6 months (95% CI: [42.4-66.4]) is obtained for PROFILE 1001 (53 patients). For OxOnc (127 patients), the median PFS follow-up is 21.3 months (95% CI: [18.7-21.5]).

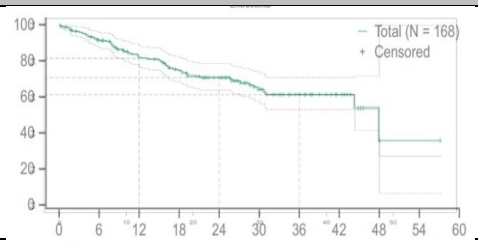
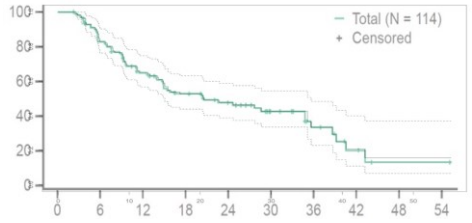
Indirect treatment comparisons

A7. Please provide details of the digitisation software used to reconstruct PFS, OS and DOR individual patient data from the entrectinib Kaplan-Meier curves (CS, Appendix D, p 32) and please comment on the accuracy of the recreated Kaplan-Meier curves (CS, Figure 6, Figure 7, and Figure 8, respectively) versus the published curves.

The Kaplan-Meier curves were digitised using the software WebPlotDigitizer (https://apps.automeris.io/wpd4/) which extracts coordinates of the curves. The Guyot algorithm was then used on R to reconstruct the individual patient data. The published Kaplan-Meier curves and the reconstructed curves were visually compared and the median OS/PFS/DOR as well as number of events were estimated to assess their similarities with published data. Table 6 below summarises the reconstructed data compared to published evidence.

Table 6. Quality assessment of the digitised curves compared to published evidence

Outcome	Source of data	Number of events	Median [95% CI]	Curves
PFS	Published	105	15.7 [12.0-21.1]	
	Reconstructed	104	15.9 [12.1-21.3]	

Outcome	Source of data	Number of events	Median [95% CI]	Curves
OS	Published	54	47.8 [44.1-NE]	
	Reconstructed	53	47.9 [44.3-NE]	
DOR	Published	64	20.5 [14.8-34.8]	
	Reconstructed	64	20.5 [15.0-35.6]	

Abbreviations: DOR: duration of response; OS: overall survival; PFS: progression-free survival

A8. Please clarify the crizotinib and entrectinib sample sizes included in the OS, PFS and DOR STCs (CS, Section 3.12).

No restriction was applied to the crizotinib trials before conducting the STCs, therefore the full population with data available for this outcome was considered. The sample sizes are reported in Table 7 below.

Table 7. Sample sizes used per trial for the STCs

Outcome	Crizotinib (sample size)			Entrectinib (pooled sample size from ALKA-372-001, STARTRK-1 and STARTRK-2)
	PROFILE 1001	OxOnc	Pooled	
OS	53	127	180	168
PFS	53	127	180	168
DOR	38	91	129	114

A9. Priority question. The company states that "time-varying HRs have been calculated" (CS, Appendix D, p32) and that "different time points as well as an average HR over the observed follow-up were estimated" (CS, Appendix D, p32). Please provide further details of the time-varying HR approach, specifically:

a) **the methodology used to generate the time-varying HRs (including the average HR) after fitting parametric survival models to the data**
b) **the 95% confidence intervals for the average HRs for PFS, OS and DoR**

c) the programming code used to estimate the time-varying HRs and average HRs and associated 95% confidence intervals.

a) After fitting the parametric survival models to the data, the hazard rates were computed per arm, using the hazard function for the selected distribution per outcome of interest, i.e., lognormal for OS, Gompertz for PFS and Generalised Gamma for DoR, from the *flexsurv* package in R. The adjusted hazard rate of crizotinib was then divided by the hazard rate from entrectinib to obtain the time-varying HRs of crizotinib versus entrectinib. The average HR was computed as the mean time-varying HRs for a specific timeframe (i.e., 0 to 7 years).

b) Initially, the 95% confidence intervals for the average HRs for PFS, OS and DOR were not computed because for OS and DOR, after 3 years and 2 years respectively, the lower limit of the 95% confidence interval is estimated at exactly 0. Calculating the average interval requires taking the natural logarithm of 0, which is not defined. For that reason, we provided the 95% confidence intervals for specific time points (i.e. 1 year, 2 years…), using the *standsurv* function from the *flexsurv* package in R. The standard error of the HR at specific time point was computed as:

$$se_{HR_t} = \sqrt{\left(\frac{se_{h_{crizotinib_t}}}{h_{crizotnib_t}}\right)^2 + \left(\frac{se_{h_{entrectinib_t}}}{h_{entrectinib_t}}\right)^2}$$

Per request, we revisited the calculations, and we present here the average HR and accompanying 95% confidence interval using the Delta method. For PFS, it is an average up to 7 years, for OS up to 3 years, and for DOR up to 2 years.

Table 8 Average HRs and 95% confidence intervals for OS, PFS and DOR

Outcome	Average HR [95% CI]
OS	[redacted] – up to 3 years
PFS	[redacted] – up to 7 years
DOR	[redacted] – up to 2 years

Abbreviations: CI: confidence interval; DOR: duration of response; HR: hazard ratio, OS: overall survival; PFS: progression-free survival

c) Please find below the programming code used to estimate the time-varying HRs and associated 95% confidence intervals along with the and average HRs for OS:

```
#Create a sequence of 1000 points, corresponding to time between 0 and 84
months
times_1k <- seq(84/1000, 84, length.out = 1000)

#Create a sequence of time, corresponding to every year between 1 and 7
years
times_y <- seq(12,84,by=12)

#Fit the model with the distribution of interest and covariates of interest
on the crizotinib IPD; distribution = lognormal and 3 selected covariates,
i.e., ECOG PS, age and smoking status
model.selected <- flexsurvreg(Surv(Time, Event) ~ ECOG0.bin +
AGE_more54.bin + SMKCLAS,

                  data = data,

                  dist = "lnorm")

#Adjust the hazard rate of crizotinib based on the marginal values of
patient characteristics from the pooled studies of entrectinib
coeffs <- model.selected$coefficients

var    <- coeffs[which(!names(coeffs) %in% c("shape", "rate"))]

meanlog.crizo  <-   coeffs["meanlog"][[1]] +

                    coeffs["AGE_more54.bin"][[1]] *
baseline.agd["AGE_more54>= 54"][[1]]+

                    coeffs["ECOG0.bin"][[1]] * baseline.agd["ECOG0.bin1"]
[[1]]+

                    coeffs["SMKCLASNEVER SMOKED"][[1]]*
baseline.agd["SMKCLASNEVER SMOKED"] [[1]]

haz_crizo =  hlnorm(times_10k,

                    meanlog  = meanlog.crizo,

                    sdlog = exp(coeffs["sdlog"]),

                    log = FALSE)

haz_crizo_y = hlnorm(times_y,

                    meanlog  = meanlog.crizo,

                    sdlog = exp(coeffs["sdlog"]),

                    log = FALSE)

#Compute the standard error of the adjusted crizotinib hazard rate for
specific time points
```

```
newdata <- data %>% mutate(AGE_more54.bin = rbinom(180, 1,
agd_IPD.df["AGE_more54>= 54"][[1]]),

                      ECOG0.bin = rbinom(180, 1,
agd_IPD.df["ECOG0.bin1"][[1]]),

                      SMKCLAS = rbinom(180, 1, agd_IPD.df["SMKCLASNEVER
SMOKED"][[1]])) %>%

  mutate(SMKCLAS = as.factor(ifelse(SMKCLAS == 1, "NEVER SMOKED", "EX
SMOKER")))

se_crizo_y <- standsurv(model.selected, type = "hazard", t = times_y, se =
TRUE, newdata = newdata)

#Fit the model with the distribution of interest on the reconstructed AgD;
distribution = lognormal
model_entrectinib <- flexsurvreg(as.formula("Surv(Time, Event) ~ 1"),

                 data = PFS_entrectinib,

                 dist = distribution) # KEEP THE SAME DISTRIBUTION AS FOR
IPD

#Compute the hazard rate of the entrectinib arm
coeff <- model_entrectinib$coefficients

haz_entr =  hlnorm(times_10k,

                    meanlog  = coeff["meanlog"],

                    sdlog = exp(coeff["sdlog"]),

                    log = FALSE)

haz_entr_y = hlnorm(times_y,

                    meanlog  = coeff["meanlog"],

                    sdlog = exp(coeff["sdlog"]),

                    log = FALSE)

#Compute the standard error of the hazard rate for the entrectinib arm
se_entr_y = standsurv(model_entrectinib, type = "hazard", t = times_y, se =
TRUE)

#Compute the time-varying hazard ratios by dividing the two hazard rates
HR1 <- data.frame(

  months = times_1k,

  HR = haz_crizo / haz_entr)

#Compute the standard error of the HR for specific timepoints
se_HR_y <- data.frame(time = times_y, se =
sqrt((se_crizo_y$at1_se/se_crizo_y$at1)**2 +
(se_entr_y$at1_se/se_entr_y$at1)**2))
```

```
#Combine the HR and 95% CI with the average HR for specific timepoints
HR_y <- data.frame (

  Months = times_y,

  HR = round(haz_crizo_y / haz_entr_y,digits = 2),

  HR_Average = round( tapply(HR1$HR, ceiling(seq_along(HR1$HR) / (1000/7)),
mean), digits = 2)) %>%

  mutate(HR = paste0(HR, " [", round(ifelse(HR-1.96*se_HR_y$se>0, HR-
1.96*se_HR_y$se, 0), 2), "; ", round(HR+1.96*se_HR_y$se, 2), "]"))


#Calculate the average HR and accompanying 95%CI using the Delta method

# OS

# keep only 3 years as problem with lower limit of 0

HRs <- c([redacted])

lower_CIs <- c([redacted])

upper_CIs <- c([redacted])

intervals <- rep(12, 3)  # Each interval is 12 months

# Function to calculate the average HR and its 95% CI

calculate_average_hr <- function(HRs, lower_CIs, upper_CIs, intervals) {

  # Calculate the log HRs and their variances

  log_HRs <- log(HRs)

  log_lower_CIs <- log(lower_CIs)

  log_upper_CIs <- log(upper_CIs)

  # Calculate the variances of the log HRs

  log_HR_vars <- ((log_upper_CIs - log_lower_CIs) / (2 * 1.96))^2

  # Calculate the weighted average of log HRs

  weighted_log_HRs <- sum(log_HRs * intervals) / sum(intervals)

  # Calculate the variance of the weighted average log HR

  weighted_var_log_HR <- sum(log_HR_vars * intervals^2) / sum(intervals)^2

  # Back-transform to get the average HR

  average_HR <- exp(weighted_log_HRs)

  # Calculate the 95% CI for the average HR

  lower_95_CI <- exp(weighted_log_HRs - 1.96 * sqrt(weighted_var_log_HR))
```

```
  upper_95_CI <- exp(weighted_log_HRs + 1.96 * sqrt(weighted_var_log_HR))


 return(list(average_HR = average_HR, lower_95_CI = lower_95_CI,
upper_95_CI = upper_95_CI))

}

# Perform the calculation

resultOS <- calculate_average_hr(HRs, lower_CIs, upper_CIs, intervals)

# Print the results

cat("Average HR:", resultOS$average_HR, "\n")

cat("95% CI: [", resultOS$lower_95_CI, ", ", resultOS$upper_95_CI, "]\n")


##------------------------------------------------------------------------
----------------------------------------------##

# PFS

# Create dataset with point estimates and CIs per time interval

HRs <- c([redacted])

lower_CIs <- c([redacted])

upper_CIs <- c([redacted])

intervals <- rep(12, 7)  # Each interval is 12 months

# Function to calculate the average HR and its 95% CI

calculate_average_hr <- function(HRs, lower_CIs, upper_CIs, intervals) {

  # Calculate the log HRs and their variances

  log_HRs <- log(HRs)

  log_lower_CIs <- log(lower_CIs)

  log_upper_CIs <- log(upper_CIs)

  # Calculate the variances of the log HRs

  log_HR_vars <- ((log_upper_CIs - log_lower_CIs) / (2 * 1.96))^2


  # Calculate the weighted average of log HRs

  weighted_log_HRs <- sum(log_HRs * intervals) / sum(intervals)

  # Calculate the variance of the weighted average log HR
```

```
  weighted_var_log_HR <- sum(log_HR_vars * intervals^2) / sum(intervals)^2

  # Back-transform to get the average HR

  average_HR <- exp(weighted_log_HRs)

  # Calculate the 95% CI for the average HR

  lower_95_CI <- exp(weighted_log_HRs - 1.96 * sqrt(weighted_var_log_HR))

  upper_95_CI <- exp(weighted_log_HRs + 1.96 * sqrt(weighted_var_log_HR))

  return(list(average_HR = average_HR, lower_95_CI = lower_95_CI,
upper_95_CI = upper_95_CI))

}


# Perform the calculation

resultPFS <- calculate_average_hr(HRs, lower_CIs, upper_CIs, intervals)

# Print the results

cat("Average HR:", resultPFS$average_HR, "\n")

cat("95% CI: [", resultPFS$lower_95_CI, ", ", resultPFS$upper_95_CI, "]\n")


##------------------------------------------------------------------------
----------------------------------------------##

# DOR

# Create dataset with point estimates and CIs per time interval

HRs <- c([redacted])

lower_CIs <- c([redacted])

upper_CIs <- c([redacted])

intervals <- rep(12, 2)  # Each interval is 12 months

# Function to calculate the average HR and its 95% CI

calculate_average_hr <- function(HRs, lower_CIs, upper_CIs, intervals) {

  # Calculate the log HRs and their variances

  log_HRs <- log(HRs)

  log_lower_CIs <- log(lower_CIs)

  log_upper_CIs <- log(upper_CIs)

  # Calculate the variances of the log HRs
```

```
  log_HR_vars <- ((log_upper_CIs - log_lower_CIs) / (2 * 1.96))^2

  # Calculate the weighted average of log HRs

  weighted_log_HRs <- sum(log_HRs * intervals) / sum(intervals)

  # Calculate the variance of the weighted average log HR

  weighted_var_log_HR <- sum(log_HR_vars * intervals^2) / sum(intervals)^2

  # Back-transform to get the average HR

  average_HR <- exp(weighted_log_HRs)

  # Calculate the 95% CI for the average HR

  lower_95_CI <- exp(weighted_log_HRs - 1.96 * sqrt(weighted_var_log_HR))

  upper_95_CI <- exp(weighted_log_HRs + 1.96 * sqrt(weighted_var_log_HR))

  return(list(average_HR = average_HR, lower_95_CI = lower_95_CI,
upper_95_CI = upper_95_CI))

}


# Perform the calculation

resultDOR <- calculate_average_hr(HRs, lower_CIs, upper_CIs, intervals)

# Print the results

cat("Average HR:", resultDOR$average_HR, "\n")

cat("95% CI: [", resultDOR$lower_95_CI, ", ", resultDOR$upper_95_CI, "]\n")
```

A10. The company states "Key differences across studies were noted in terms of ethnicity, ECOG PS, histological classification, number of prior regimens, age, and baseline CNS lesions" (CS, Appendix D, p30), please clarify:

- **a) why only six covariates were identified for inclusion in the ITC**
- **b) whether clinicians were consulted over the identification of prognostic factors**
- **c) please clarify why the 'full model' with all covariates was not considered as the base case analysis.**

a) A total of nine variables were identified for inclusion in the ITC as potential prognostic factors and treatment effect modifiers. Among these, we excluded covariates for which the adjustment of crizotinib on entrectinib was not possible due to data not being fully reported (i.e., when the modalities of certain

covariates were reported in only one treatment arm). This exclusion applies to: disease stage, baseline CNS lesions and number of prior regimens. Thus, the full model includes the remaining covariates age, sex, ethnicity, ECOG PS, smoking status and histological classification.

b) Prognostic factors were identified through a literature review on prognostic factors and TEMs (based on hand searches) and a review of subgroup analyses conducted in the studies of interest (based on the SLR). Additionally, we reviewed the list of factors in the single technology appraisal of entrectinib in the same indication, where the selection was informed by clinical experts.[16] From that list, we included all covariates except for disease stage and prior treatments, due to data not being fully reported. The common covariates considered in both appraisals are then: age, ECOG PS, ethnicity and smoking history.

c) The model considered as the base-case analysis was the one that provided the best fit to the data based on two goodness-of-fit metrics (Akaike Information Criterion and Bayesian Information Criterion). Thus, the full model was not automatically used as base-case but is still included as a sensitivity analysis.

A11. The company states that an "STC was selected as the base case methodology over MAIC based on poor overlap of population in terms of ethnicity" and "To avoid a highly reduced effective sample size, an STC was considered an appropriate approach" (CS, Section 3.12, p63):

a) please clarify why ethnicity was not included in the base case STC

b) please clarify why the STC approach was selected over a MAIC despite the base case STC including only three covariates.

a) As part of the STC development, two models were considered: the full model, which aimed to adjust for all reported prognostic factors and treatment effect modifiers, and a restricted model, including a subset of selected variables based on goodness of fit metrics. The base case STC was thus defined as the best model in terms of model fit to potentially reduce the standard error of the estimated coefficients, and this model was found to include only three covariates. However, given the expected potential bias of not adjusting for all

prognostic factors and treatment effect modifiers when considering unanchored comparisons, the full model was still considered as a sensitivity analysis. Both models were consistent in estimates obtained, i.e., direction and magnitude of the relative effect favouring crizotinib, with the full model producing slightly more pronounced effect.

b) STC was preferred over MAIC for methodological and comparison-specific reasons. From a methodological standpoint, recent simulation results have shown that MAIC performs poorly compared to STC, and in some scenarios it has been shown to increase bias compared to a standard indirect comparison.[17] Additionally, given the unanchored nature of the ITC, MAIC has been found to increase variation between the absolute effects, whereas STC being a regression method may reduce it.[18] Furthermore, considering that a MAIC of entrectinib vs crizotinib using a similar but not identical pool of data has been implemented in the STA of entrectinib, a base case analysis using MAIC was deemed of secondary interest, as it could lead to different results and recommendations. From a comparison standpoint, implementing a MAIC including ethnicity had a significant impact on ESS; nearly half of the sample size was reduced compared to the analysis excluding this variable (83.3 vs 158.2).

A12. Priority question. The company states that "Patient level data of OxOnc and PROFILE 1001 were pooled" (CS, Appendix D, page 31):

a) please justify why, in the ITCs, PROFILE 1001 and OxOnc trial data were pooled

b) please perform an ITC using data from the OxOnc and PROFILE 1001 trials individually, and comment on the similarity of results compared to the ITC using pooled OxOnc and PROFILE 1001 data or explain why this is not possible.

a) PROFILE 1001 and OxOnc were pooled to increase the sample size of crizotinib, and to create a population with more overlap with the entrectinib studies as OxOnc included only Asian patients.

Per request, STCs were additionally conducted separately on the individual trials following the same methodology as the one conducted on the pooled OxOnc and PROFILE 1001 datasets. For comparison and consistency purposes, we selected

the same parametric survival curve as in the pooled analysis; overall there were very small differences in the AICs across the competing survival distributions. The results are summarised for PFS (

b) Table 9), OS (Table 10), DOR (Table 11), and ORR (Table 12), respectively. The HR estimates varied across STCs conducted on the same outcome, and the confidence intervals were wider in these analyses, which was expected considering the low sample sizes. The findings from the individual analyses were overall consistent in direction and magnitude of effect compared to the pooled analysis.

Table 9. PFS STCs conducted on pooled PROFILE 1001 and OxOnc, as well as per individual trial

Trials, distribution and covariates	Pooled PROFILE 1001 & OxOnc		PROFILE 1001		OxOnc	
	Distribution: Log-normal		Distribution: Log-normal		Distribution: Log-normal	
	Covariates included: smoking status, ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1), age group (>=54)	
Months	HR [95% CI]	Average HR	HR [95% CI]	Average HR	HR [95% CI]	Average HR
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; STC: simulated treatment comparison

Table 10. OS STCs conducted on pooled PROFILE 1001 and OxOnc, as well as per individual trial

Trials, distribution and covariates	Pooled PROFILE 1001 & OxOnc		PROFILE 1001		OxOnc	
	Distribution: Gompertz		Distribution: Gompertz		Distribution: Gompertz	
	Covariates included: smoking status, ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1), age group (>=54)	
Months	HR [95% CI]	Average HR	HR [95% CI]	Average HR	HR [95% CI]	Average HR
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; STC: simulated treatment comparison

Table 11. DOR STCs conducted on pooled PROFILE 1001 and OxOnc, as well as per individual trial

Trials, distribution and covariates	Pooled PROFILE 1001 & OxOnc		PROFILE 1001		OxOnc	
	Distribution: Generalized Gamma		Distribution: Generalized Gamma		Distribution: Generalized Gamma	
	Covariates included: ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1)		Covariates included: sex, ECOG score (>=1), age group (>=54)	
Months	HR [95% CI]	Average HR	HR [95% CI]	Average HR	HR [95% CI]	Average HR
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trials, distribution and covariates	Pooled PROFILE 1001 & OxOnc		PROFILE 1001		OxOnc	
	Distribution: Generalized Gamma		Distribution: Generalized Gamma		Distribution: Generalized Gamma	
	Covariates included: ECOG score (>=1), age group (>=54)		Covariates included: smoking status, ECOG score (>=1)		Covariates included: sex, ECOG score (>=1), age group (>=54)	
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DOR: duration of response; HR: hazard ratio; STC: simulated treatment comparison

Table 12. ORR STCs conducted on pooled PROFILE 1001 and OxOnc, as well as per individual trial

Trials used	Covariates included	ORR [95% CI]
PROFILE 1001 and OxOnc	smoking status	[redacted]
	ECOG score (>=1)	
	age group (>=54)	
PROFILE 1001	smoking status	[redacted]
	ECOG score (>=1)	
	age group (>=54)	
OxOnc	smoking status	[redacted]
	ECOG score (>=1)	
	age group (>=54)	

Abbreviations: CI: confidence interval; OR: odds ratio; ORR: overall response rate; STC: simulated treatment comparison

A13. In CS, Appendix D 2.1, Table 13 and CS, p30, the company reports that the proportion of Asian patients from the entrectinib studies is 45.3%. However, in CS, Table 8 and CS, Appendix D, Table 27, the proportion of Asian patients from the entrectinib studies is 46.4%. Please clarify which is the correct value and which value has been used to represent the proportion of Asian patients from the entrectinib studies in the STC and in the MAIC.

The correct proportion of Asian patients from the entrectinib studies is 46.4 % (78 / 168). This value was the one used in the STC and in the MAIC. CS, Appendix D 2.1, Table 13 and CS, p30 should report 78/168 (46.4%) of Asian patients and 80/168 (47.6%) of non-Asian patients, these are errors made when extracting the data.

Section B: Clarification on cost effectiveness data

The EAG has no cost effectiveness clarification questions.

Section C: Textual clarification and additional points

C1. Please provide:

- **the PROFILE 1001 trial CSR for the June 2018 data cut-off and the TSAP**
- **the OxOnc trial CSR for the July 2020 data cut-off, the TSAP and the trial protocol.**

The requested CSRs, TSAPs and trial protocol has been provided.

C2. Please clarify whether, when carrying out the clinical effectiveness evidence SLR, data were extracted by two or more independent reviewers.

Within the clinical effectiveness evidence SLR, data extraction was carried out by one independent reviewer, and 100% of the extracted data was then quality checked by a second reviewer to ensure accuracy and consistency in the extraction and reporting of the evidence. This approach is in line with the NICE guidance for conducting SLRs.[19]

C3. The EAG considers that the ROBINS-I tool is not an appropriate quality assessment tool for the PROFILE 1001, OxOnc, METROS, EUCROSS, AcSé STARTRK-2 studies as it is intended for studies with two or more treatment groups. Please conduct a quality assessment exercise using the Critical Appraisal Skills Programme (CASP) checklist[20] for cohort studies.

Table 13 Quality assessment of studies identified in the clinical effectiveness systematic literature review using the CASP (Cohort Study) checklist

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
Section A: Are the results of the study valid?							
1	**Did the study address a clearly focused issue?**	Yes Study investigated whether crizotinib had antitumour activity in patients with advanced NSCLC with ROS1 rearrangement.	Yes Study assessed the efficacy and safety of crizotinib in East Asian patients with ROS1-positive advanced NSCLC.	Yes Study aimed at investigating activity of crizotinib in patients with locally advanced or metastatic NSCLC, pretreated with at least one previous chemotherapy line, with *MET* amplification, *MET* exon 14 mutation or *ROS1* rearrangement	Yes Study assessed efficacy and safety of crizotinib in European patients with locally advanced or metastatic NSCLC and *ROS1* rearrangement	Yes Study assessed efficacy and safety of crizotinib in patients with inoperable, historically confirmed locally advanced or metastatic NSCLC, for which no standard or curative treatment was available; with *c-MET* ≥6 copies, *c-MET*-mutated, or *ROS1*-translocated tumours	Yes Study assessed efficacy, safety and quality of life associated with entrectinib in patients with locally advanced or metastatic *NTRK1/2/3* and *ROS1* fusion-positive solid tumours
2	**Was the cohort recruited in an acceptable way?**	Yes Study participants were identified using objective and standardised measurement methods ensuring minimisation of	Yes Study participants were identified using objective and standardised measurement methods ensuring minimisation of	Yes Study participants were identified using objective and standardised measurement methods ensuring minimisation of	Yes Study participants were identified using objective and standardised measurement methods ensuring minimisation of	Yes Study participants were identified using objective and standardised measurement methods ensuring minimisation of	Can't tell The included publications lacked more detailed information on how patients matching the study population were identified:

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
		selection bias and to match the defined patient population: • Break-apart FISH and RT-PCR assay to identify ROS1 rearrangement • ECOG status of 0-2 to identify level of functioning • RECIST to measure disease • All patients provided informed consent	selection bias and to match the defined patient population: • Amoy real-time polymerase chain reaction assay to identify ROS1 rearrangement • Amoy real-time polymerase chain reaction assay, immunohistochemistry or Vysis ALK fluorescence in situ hybridization test to confirm ALK-negative status • ECOG status of 0-1 to identify level of functioning • RECIST to measure disease • All patients provided informed consent	selection bias and to match the defined patient population: • Using FISH to centrally confirm ROS1 rearrangement and MET amplification in participants • MET mutational status was centrally verified using Sanger direct sequencing • ECOG status of 0-2 to identify level of functioning • RECIST to measure disease • All patients provided informed consent	selection bias and to match the defined patient population: • Using FISH to centrally confirm ROS1 rearrangement • ECOG status of 0-2 to identify level of functioning • RECIST to measure disease • All patients provided informed consent	selection bias and to match the defined patient population: • Using IHC confirmed by FISH to centrally confirm ROS1 rearrangement • MET amplification were confirmed by FISH • MET mutational status was assessed using NGS and confirmed by Sanger sequencing • ECOG status of 0-2 to identify level of functioning • RECIST to measure disease	• Locally advanced or metastatic solid tumours with NTRK 1/2/3, ROS1 or ALK gene fusion – NR on how assessed • ECOG status of 0-2 to identify level of functioning
3	**Was the exposure accurately measured to minimise bias?**	Yes Crizotinib was administered daily in continuous 28-day cycles until RECIST-defined disease progression, clinical	Yes Crizotinib was administered daily in continuous 28-day cycles until RECIST-defined disease progression,	Yes Crizotinib was administered daily in continuous 28-day cycles until disease progression, unacceptable	Yes Crizotinib was administered daily in continuous 28-day cycles until disease progression, death, withdrawal of	Yes Crizotinib was administered daily in continuous 28-day cycles until disease progression, patient withdrawal, or for any	Yes Entrectinib was administered orally daily in 4-week cycles.

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
		deterioration, unacceptable toxic effects, withdrawal from the study or death.	unacceptable toxic effects or withdrawal from the study.	toxicity, withdrawal of consent, or death.	the informed consent, or inacceptable toxicity.	other reason in the interest of the patient.	
4	**Was the outcome accurately measured to minimise bias?**	Yes Patients underwent baseline tumour imaging via CT or MRI. Tumour assessment during treatment were performed by the study investigators every 8 weeks.	Yes Tumour assessments were performed at baseline, every 8 weeks until cycle 8 and every 12 weeks thereafter. All images were subject to review by an independent radiology laboratory, and tumour responses were assessed using RECIST version 1.1.	Can't tell Endpoints were investigator-assessed. No information on measurement methods.	Yes Efficacy assessment was performed via CT or MRI. Brain scans were mandated at baseline and during follow-up. A blinded IRR was performed for selected efficacy endpoints.	Yes Tumour response was assessed by CT-scan and/or MRI at baseline, then every 8 weeks. In addition, CT-scans and/or MRI were required when disease progression was suspected or to confirm a PR or CR.	Yes . Tumour responses were assessed by BICR per RECIST v1.1 after 4 weeks and every 8 weeks thereafter.
5a	**Have the authors identified all important confounding factors?**	Can't tell N/A	Can't tell N/A	Yes Authors compared patient characteristics in those with and without BM for • Age • Gender • Previous therapies	Can't tell N/A	Can't tell N/A	Can't tell N/A
5b	**Have they taken account of the confounding factors in the design and/or analysis?**	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
6a	**Was the follow up of subjects complete enough?**	Yes There was enough time to reveal good and bad effects. Leaving the study was due to treatment discontinuation due to AEs in 2% of patients (1/50)[8] and death in 49% of patients (26/53).[4]	Yes There was enough time to reveal good and bad effects. Leaving the study was due to treatment discontinuation due to AEs in 2.4% (3/127) of patients and death in 51.2% of patients (65/127).[9]	Yes There was enough time to reveal good and bad effects. Leaving the study was due to death in 31.2% of patients (15/48).[22]	Yes There was enough time to reveal good and bad effects. Leaving the study was due to death which was observed in 43.8% of patients (28/64).[24]	Can't tell No judgment possible on whether follow-up time was sufficient enough to reveal good and bad effects as median follow-up time was not reported. Leaving the study was due to treatment discontinuation due to AEs in 8.1% (3/37) of patients.	Yes There was enough time to reveal good and bad effects. Leaving the study was due to treatment discontinuation due to AEs in 21.7% (5/23) of patients[27], death in 31% (83/268) of patients, consent withdrawal in 0.09% (23/268) of patients, loss to follow-up in 0.01% (3/268) of patients or other reasons in 0.01% (2/180) of patients.[26]
6b	**Was the follow up of subjects long enough?**	Yes Median duration of follow-up was 62.6 months.[4]	Yes Median duration of follow-up was 56.1 months.[9]	Yes Median follow-up was 54.4 months.[23]	Yes Median follow-up was 55.9 months.[24]	Can't tell Median follow-up was not reported.	Yes Median survival follow-up was reported at 38.6 months in Murakami 2022.[27]
Section B: What are the results?							
7	**What are the results of this study?**	Results supported the clinically meaningful effectiveness and safety of crizotinib in patients with *ROS1*-rearranged NSCLC.	Results supported the clinically meaningful effectiveness and safety of crizotinib in East Asian patients with *ROS1*-rearranged NSCLC.	Results supported the clinically meaningful effectiveness and safety of crizotinib in the *ROS1* cohort. No difference in any clinical endpoint was	Results supported the clinically meaningful effectiveness and safety of crizotinib in patients with *ROS1*-rearranged NSCLC. Two patients with ROS1 wild-type sequences	Results supported the clinically meaningful effectiveness of crizotinib in patients with *ROS1*-rearranged NSCLC. The ORR was 16% in the *c-MET*≥6 copies	Results supported the clinically meaningful effectiveness and safety of entrectinib in patients with locally advanced/ metastatic *ROS1* fp NSCLC and *NTRK*-fp solid tumours.

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
		Results were reported as proportions (ORR, AEs, survival probabilities) and median length of response in months (DOR, PFS, OS).	Results were reported as proportions (AEs, probability of survival, QoL, DOR) and median length of response in months (OS).	observed between *MET*-amplified and exon 14–mutated patients. No response was observed among the five patients with cooccurrence of a second gene alteration. No unexpected toxicity was observed in both cohorts Results were reported as proportions (ORR) and median length of response in months (PFS, OS).	assessed by DNA sequencing had progression as best response. CD74-ROS1-positive patients had a trend towards a higher ORR and longer median PFS. TP53-co-mutant patients had a significantly shorter median PFS than wild-type patients. Results were reported as proportions (ORR, AEs, DCR), median length of response in months (PFS, OS) and mean scores (QoL).	cohort, 10.7% in the mutated, and 47.2% in the *ROS1* cohort. The best ORR during treatment was 32% in the c-*MET*≥6 copies cohort, 36% in the c-*MET*-mutated, and 69.4% in the *ROS1*-translocation cohort. Results were reported as proportions (ORR, BOR) and median length of response in months (PFS, OS).	Results were reported as proportions (ORR, OS, TRAEs, AEs) and mean scores (QoL).
8	**How precise are the results?**	Precise, CIs did not cross nil.	Precise, CIs did not cross nil.	Precise, CIs did not cross nil.	Precise, CIs did not cross nil.	Precise, CIs did not cross nil.	Precise, CIs did not cross nil.
9	**Do you believe the results?**	Yes Even though there is not further information on adjustment for potential confounding, the measurement of exposure and	Yes Even though there is not further information on adjustment for potential confounding, the measurement of exposure and	Yes Even though there has been limited information given on the adjustment for potential confounding, the measurement of exposure and outcome have been	Yes Even though there is not further information on adjustment for potential confounding, the measurement of exposure and outcome have been described in detail	Yes Even though there is not further information on adjustment for potential confounding, the measurement of exposure and outcome have been described in detail	Yes Even though there is not further information on adjustment for potential confounding, the measurement of exposure and outcome have been described in detail

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
		outcome have been described in detail and have been measured via objective measurement methods. CIs do not cross nil.	outcome have been described in detail and have been measured via objective measurement methods. CIs do not cross nil.	described in detail and have been measured via objective measurement methods. CIs do not cross nil.	and have been measured via objective measurement methods. CIs do not cross nil.	and have been measured via objective measurement methods. CIs do not cross nil.	and have been measured via objective measurement methods. CIs do not cross nil.
Section C: Will the results help locally?							
10	**Can the results be applied to the local population?**	Yes	Yes	Yes	Yes	Yes	Yes
		While no RCTs evaluating crizotinib and entrectinib are available, the included studies are comparable and appropriate in terms of quality to well-performed RCTs, given the rarity of this specific tumour posing challenges in conducting large RCTs. Study subjects were similar to those in the general population.					
11	**Do the results of this study fit with other available evidence?**	Yes	Yes	Yes	Yes	Yes	Yes Results of the pooled analysis of ALKA-372-001, STARTRK-1 and STARTRK-2 showed that entrectinib has a clinically meaningful benefit in ROS1-positive advanced NSCLC patients.
		Results of crizotinib studies included in this assessment align and all demonstrated that crizotinib shows a clinically meaningful benefit in ROS1-positive advanced NSCLC patients.					
12	**What are the implications of this study for practice?**	The study findings serve as a new benchmark for OS in ROS1-rearranged advanced NSCLC and continue to show the clinically meaningful benefit and safety of crizotinib in this molecular subgroup.	Findings serve as a new benchmark for OS in East Asian patients. The QoL and safety profile with long-term follow-up were consistent with previous reports and support the continued use of crizotinib in the	Crizotinib has been found highly effective in the *ROS1* cohort. It has induced a response in a fraction of MET-deregulated NSCLC. Additional studies and innovative therapies are urgently needed.	Crizotinib is highly effective and safe in patients with ROS1-rearranged lung cancer. ROS1-/TP53-coaberrant patients had a significantly worse outcome compared to TP53 wild-type patients.	Crizotinib activity in patients with *ROS1*-translocated tumours was confirmed. In the *c-MET*-mutation and *c-MET*≥6 copies cohorts, despite insufficient ORR after two cycles of crizotinib, there are signs of late response not sufficient to justify	Entrectinib showed deep and durable responses and manageable safety in Japanese patients with locally advanced/ metastatic ROS1-fp NSCLC or NTRK-fp solid tumours. PRO findings were consistent with the

CASP Checklist Questions		Crizotinib					Entrectinib
		PROFILE 1001 (NCT00585195) Shaw, 2019[4] Shaw, 2014[8]	**OxOnc (NCT01945021)** Wu, 2018[6] Wu, 2022[9]	**METROS (NCT02499614)** Landi, 2019[21] Chiari, 2020[22] Cappuzzo, 2022[23]	**EUCROSS (NCT02183870)** Michels, 2019[12] Michels, 2022[24]	**AcSé (NCT02034981)** Moro-Sibilot, 2019[25]	**STARTRK-2 (NCT02568267)** Paz-Ares, 2021[26] Murakami, 2022[27] Lu, 2022[28]
			treatment of patients with ROS1-positive advanced NSCLC.			the development of crizotinib in this indication. The continued targeting of c-*MET* with innovative therapies appears justified.	favourable safety profile of entrectinib, and further reinforce the positive benefit-risk profile of this treatment, indicating minimal overall treatment burden.

Abbreviations: AEs: adverse events; BICR: blinded independent central review; BM: brain metastases; BOR: best overall response rate; CI: confidence interval; CR: complete response; CT: computed tomography; DCR: disease control rate; DOR: duration of response; FISH: fluorescence in situ hybridization; fp: fusion positive; HRQoL: health-related quality of life; IHC: immunohistochemical; IRR: independent radiologic review; ITT: intention-to-treat; MET: Mesenchymal epithelial transition; MRI: magnetic resonance imaging; NGS: next-generation sequencing; NSCLC: Non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; QoL: quality of life; RCT: randomised controlled trial; RR: response rate; PROs: patient-reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumours; ROS1: Proto-oncogene tyrosine-protein kinase 1; RT-PCR: reverse-transcriptase–polymerase-chain-reaction; TRAEs: treatment-related adverse events; TTD: Time to treatment discontinuation; vs: versus

C4. Please conduct a quality assessment exercise for the Drilon 2022[5] pooled analysis of the ALKA-372-001, STARTRK-1 and STARTRK-2 studies.

Study quality of the pooled (integrated) analysis of the three entrectinib studies (ALKA-372-001, STARTRK-1 and STARTRK-2) reported by Drilon 2022 was assessed using the Downs and Black checklist.[5,29] In line with TA643, this checklist was considered the most relevant as it has been previously reviewed and accepted by NICE.[16]

Table 14 Quality assessment of pooled analysis by Drilon 2022

Downs and Black checklist questions		ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[5]	
		Yes / No / NA / Unable to determine	Comment
Reporting			
1	Is the hypothesis/aim/objective of the study clearly described?	Yes	-
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	ORR, DOR, PFS, OS, safety
3	Are the characteristics of the patients included in the study clearly described?	Yes	Adult patients (aged ≥18 years) with locally advanced or metastatic ROS1 fusion-positive NSCLC
4	Are the interventions of interest clearly described?	Yes	Entrectinib at a dose of at least 600 mg orally once per day
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	NA	-
6	Are the main findings of the study clearly described?	Yes	Results reported separately for an efficacy-assessable population (n=168), and a safety population (n=224)
7	Does the study provide estimates of the random variability in the data for the main outcomes?	No	-
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Focus on treatment-related adverse events, with grade 1-2 events in ≥10% of patients, and all grade 3 or 4 events reported from a safety analysis set.
9	Have the characteristics of patients lost to follow-up been described?	No	-
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	NA	-
External validity			
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	-
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes	-
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	-

Downs and Black checklist questions		ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[5]	
		Yes / No / NA / Unable to determine	Comment
Internal validity-bias			
14	Was an attempt made to blind study subjects to the intervention they have received?	No	-
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	ORR, DOR and PFS were assessed by BICR.
16	If any of the results of the study were based on "data dredging", was this made clear?	NA	-
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes	Note that all studies were single-arm, and patients with a minimum of 12 months or longer follow-up were included in the analysis.
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes	-
19	Was compliance with the intervention/s reliable?	Yes	-
20	Were the main outcome measures used accurate (valid and reliable)?	Yes	-
Internal validity-selection bias			
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	-
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	-
23	Were study subjects randomised to intervention groups?	NA	-
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	-
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	NA	-
26	Were losses of patients to follow-up taken into account?	Yes	Patients with a minimum of 12 months or longer follow-up were included in the analysis. ORR, DOR and PFS were assessed by BICR.
Power			
27	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%?	NA	-

Abbreviations: BICR: blinded independent central review; DOR: duration of response; NA: not applicable; PFS: progression-free survival; ORR: objective response rate

C5. Please provide the SLR methods (including search strategies) used to identify cost effectiveness studies.

Economic data inputs informing the cost comparison analysis in this submission were sourced via desk research involving targeted searches of relevant data sources, as presented in Section B.4.2, Appendix G and Appendix H. Selection of

data and associated assumptions were also based on several previous appraisals by NICE including TA529, TA643 and TA836.[10,16,30]

C6. Please clarify whether the following cross-references to Appendix D are correct:

- **"list of prognostic factors and treatment effect modifiers identified from the literature (list available in Appendix D, Table 10)" (CS, p63); the EAG suggests that Appendix D, Table 12 should be cross-referenced**
- **"The PFS HR crizotinib vs. entrectinib over time was computed (see Appendix D, Figure 4 and Appendix D, Table 15)." CS, p64; the EAG suggests that Appendix D, Table 17 should be cross-referenced**
- **"The OS HR of crizotinib vs. entrectinib over time was computed and decreased over time (see Appendix D, Figure 9 and Appendix D, Table 19)" (CS, p66); the EAG suggests that Appendix D, Table 21 should be cross-referenced**
- **"[redacted] (see Appendix D, Figure 14 and Appendix D, Table 23)." (CS, p68) the EAG suggests that Appendix D, Table 25 should be cross-referenced**

Thank you for identifying, indeed all of these cross-references were not updated and should be replaced by the ones suggested above by the EAG.

Additional corrections identified by the company

- In Section B.3.13.2, Table 21, Drilon 2022 should also be included as it reported discontinuations due to treatment-related adverse events, as presented in the table below. The corresponding text is updated to "In two entrectinib studies, discontinuation due to TRAEs ranged from 5% to 21.7%."[5,27]

Tx	Study name Data source(s)	Patient group	Median follow-up (months)	Number of patients	Treatment discontinuations due to AEs, n (%)
Entrectinib	**ALKA-372-001, STARTRK-1, STARTRK-2 Drilon, 2022[5]**	ROS1-positive NSCLC: safety population	29.1	224	Due to TRAE: 12 (5)

- In Section B.3.3.1, Table 7, the clinical data cut-off dates for Drilon 2022 and Dziadziuszko 2021 should be updated to August 31, 2020 and May 2019, respectively.[5,7]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID6289]

NICE medicines optimisation briefing

January 2024

Advice

A full single technology appraisal of crizotinib for ROS1-positive advanced non-small-cell lung cancer (NSCLC) is unlikely to add value. A fast-track appraisal with a cost comparison comparing crizotinib with entrectinib is likely to be appropriate. However, there is no published trial directly comparing crizotinib with entrectinib, and the existing single-arm study of crizotinib is small with significant uncertainty for study outcomes.

Rationale

Crizotinib was appraised by NICE in 2018 (TA529) and was recommended for use within the Cancer Drugs Fund. Crizotinib (a protein kinase inhibitor [PKI]) may show similar clinical efficacy and safety to entrectinib, which is another PKI recommended in technology appraisal guidance (TA643) for ROS1-positive advanced NSCLC at the same point in the treatment pathway. However, this is based on limited single-arm trial evidence, which had low inclusion of people with ROS1 mutation who were treatment naïve. A randomised trial of crizotinib compared with entrectinib is in progress (NCT04603807) but is not expected to publish before 2027. Indirect comparisons of single-arm trials suggest similar clinical outcomes with crizotinib and entrectinib, including for overall survival. However, there was uncertainty in the results (reflected in wide confidence intervals) and the authors also highlight differences between the different trial populations, and between the ROS1-positive crizotinib trial population and the real-world population of people with ROS1-positive advanced NSCLC.

Technology overview

Crizotinib is a PKI licensed as monotherapy for the treatment of adults with ROS1-positive advanced NSCLC (summary of product characteristics [SPC] for crizotinib).

Context

Crizotinib as monotherapy is recommended for use through the Cancer Drugs Fund for treating ROS1-positive advanced NSCLC in adults, only if the conditions in the managed access agreement are followed (TA529 2018). Data collection for the managed access agreement ended in April 2023. The update of TA529 is the subject of this review [ID6289]. NICE has approved one other PKI, entrectinib, as monotherapy for treating ROS-1 positive NSCLC (TA643 2020). Both crizotinib and entrectinib are recommended as first-line treatment for ROS-1 positive non-squamous NSCLC (see the NICE pathway for ROS-1 positive non-squamous non-small-cell lung cancer).

NSCLC accounts for 80 to 90% of lung cancers. There are 3 histological subtypes of NSCLC: squamous-cell carcinoma, large-cell carcinoma, and adenocarcinoma, which is the most common. Adenocarcinoma and large-cell carcinoma are classified as non-squamous histological subtypes of NSCLC. ROS1 is a rare type of mutation (occurring in only 1 to 2% of people) found almost exclusively in non-squamous NSCLC.

Most lung cancers are diagnosed at an advanced stage, and the prognosis is often poor. Only 15% of patients with lung cancer in the UK survive for 5 years or more, but for those with the most advanced cancer (stage 4) only 5% will survive for more than 5 years. Targeted ROS1 therapies (crizotinib or entrectinib) reduce side effects compared with cytotoxic chemotherapy and offer improved quality of life.

Table 1: Characteristics of crizotinib compared with entrectinib

	Crizotinib	Entrectinib
Mechanism of action	Crizotinib is a selective small-molecule inhibitor of the ALK-receptor tyrosine kinase (RTK)	Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB

	and its oncogenic variants. It is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK, ROS1 (c-ros) and Recepteur d'Origine Nantais (RON) RTK.	and TRKC, proto-oncogene tyrosine-protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK).
Indication	As monotherapy for the treatment of adults with ROS1-positive advanced NSCLC.	As monotherapy for the treatment of adults with ROS1-positive advanced NSCLC not previously treated with ROS1 inhibitors.
Technology appraisal recommendation	Crizotinib is recommended for use within the Cancer Drugs Fund as an option for treating ROS1--positive advanced NSCLC in adults.	Entrectinib is recommended, within its marketing authorisation, as an option for treating ROS1-positive advanced NSCLC in adults who have not had ROS1 inhibitors.
Dosage and route of administration	250 mg twice daily (500 mg daily) (available as 200 and 250 mg oral capsules).	600 mg once daily (available as 100 or 200 mg oral capsules).
Resource impact	ROS1-positive status to be established prior to initiation. Oral treatment: convenient, non-invasive.	ROS1-positive status to be established prior to initiation. Oral treatment: convenient, non-invasive.

Current practice

Medicines for treating ROS1-positive NSCLC are commissioned by NHS England. In line with the NICE treatment options summary for ROS-1 positive non-squamous NSCLC, both crizotinib and entrectinib are commissioned as first-line options. System intelligence from NICE associates suggests that in practice entrectinib is preferred first line, partly due to the anticipated benefit for treating and preventing advanced disease with central nervous system (CNS) metastases. However, choice is based on individual patient or disease characteristics. There may be some instances where chemotherapy is initiated first line if there is clinical urgency to treat, but this is less preferred. On disease progression, options include chemotherapy or immunotherapy plus chemotherapy. Testing for ROS1 status is currently being undertaken at diagnosis, in line with the national genomic test directory. Genomic testing is seen as essential to ensure appropriate choice of treatment.

Factors for decision making

Effectiveness

Crizotinib was appraised by NICE in 2018 and was recommended for use within the Cancer Drugs Fund. Crizotinib was not recommended for routine commissioning because of uncertainty in survival benefit.

The evidence supporting the NICE technology appraisal (TA529) for crizotinib for the treatment ROS1-positive advanced NSCLC came from a small (n=53), single-arm study that included mostly people (n=46) with previously treated disease (PROFILE 1001). Follow up was for a median of 25.4 months. Median overall survival data were not mature at the time of analysis, and median progression-free survival was 19.8 months.

There is no published trial which directly compares crizotinib with the other NICE approved PKI, entrectinib. Such a trial is in progress (NCT04603807), but is not expected to publish before 2027. However, 2 studies indirectly compare crizotinib with entrectinib in ROS1-positive NSCLC.

A matched-adjusted indirect comparison by Chu et al. 2020 included aggregate crizotinib data from PROFILE 1001, NICE TA529, an analysis by Flatiron Healthcare and pooled individual patient data from 3 studies of entrectinib (2 Phase I studies ALKA-372-001 and STARTRK-1; and a single-arm Phase II basket study, STARTRK-2). This informed a 3-scenario analysis based on different percentages of CNS metastases (scenario 1: 18.1%; scenario 2: 24.64% and scenario 3: 43.4% for efficacy analyses and 50% for safety analyses; the percentages were taken from published literature).

Chu et al. (2020) found no significant differences in overall survival between entrectinib and crizotinib across the 3 scenarios (hazard ratio [HR] for scenario 1: 0.47 (95% confidence interval [CI] 0.11 to 1.03); HR for scenario 2: 0.50 (0.13 to 1.06); HR for scenario 3: 0.61 (0.16 to 1.27)). For the outcome of progression-free survival, the authors reported that it was uncertain if this was a blinded independent central review (BICR) or investigator assessed (IA) in the PROFILE 1001 study;

therefore both assumptions were tested. When a BICR was assumed, there were no statistically significant differences between entrectinib and crizotinib. When IA was assumed, the first 2 scenarios were also not statistically significantly different, but scenario 3 (assuming 43.4% CNS metastases) suggested that treatment with entrectinib may be associated with a higher risk of disease progression compared with crizotinib (HR 1.53; 95% CI 1.06 to 2.10).

A simulated treatment comparison by Tremblay et al. 2022 included individual patient data from PROFILE 1001 and aggregate data (from ALKA-372-001, STARTRK-1 and STARTRK-2) from an integrated analysis of the efficacy and safety of entrectinib (Dziadziuszko et al. 2021). Tremblay et al. (2022) also reported an updated median overall survival for the PROFILE 1001 study of 51.4 months (95% CI 29.3 to not estimable) from Shaw et al. 2019. They also compared the PROFILE 1001 data to real world evidence on crizotinib in exploratory analyses from 2 sources (Flatiron Healthcare and Ontada Oncology Insights & Technology).

In Tremblay et al. 2022, for the outcome of 12-month overall survival difference, neither the unadjusted model (risk ratio [RR] 0.98; 95% CI 0.85 to 1.11) nor the model adjusted for age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS) and smoking status (RR 1.01; 95% CI 0.90 to 1.12) were statistically significantly different between crizotinib and entrectinib. Similarly, for the outcome of median progression free survival, both the unadjusted (mean difference [MD] 3.60 months; 95% CI -9.37 to 16.57) and adjusted model (MD 3.99 months; 95% CI -6.27 to 14.25) found no statistically significant difference between crizotinib and entrectinib.

Safety

The SPC for crizotinib lists several cautions including hepatoxicity, interstitial lung disease, QT interval prolongation, bradycardia, cardiac failure (for which the MHRA have issued advice), neutropenia and leukopenia, gastrointestinal perforation, renal effects and visual effects. Cautions with entrectinib include cognitive disorders, fractures, hyperuricaemia, congestive heart failure and QT interval prolongation (SPC

for entrectinib). While most side effects of crizotinib and entrectinib are similar, and of similar frequency, there are some differences that reflect these differing cautions.

In the study by Chu et al. 2020, there were no significant differences between entrectinib and crizotinib for the outcome of discontinuation of treatment due to adverse events.

Patient centred factors

Both crizotinib and entrectinib are oral medications, although crizotinib is taken twice daily compared with once daily for entrectinib. Some people may prefer oral medicines to invasive intravenous treatments that need attendance at clinics. However, outpatient appointments for routine monitoring will still be needed for both crizotinib and entrectinib. Assessment of ROS1-positive status is recommended for both before starting treatment.

Health inequalities

Certain factors are associated with ROS1-positive lung cancer, these include younger age (median 50.5 years) than other lung cancers (more than 4 out of 10 people diagnosed with lung cancer in the UK are aged 75 and older). Female sex, with some studies reporting higher rates (64.5%) in females than males (in 2016-2018, 48% of lung cancer cases in the UK were in females and 52% were in males). However, equality impact assessments for the previous technology appraisals for crizotinib (TA529) and entrectinib (TA643) identified no overall equality issues.

Limitations of the evidence

The PROFILE 1001 study (n=53) was a single-arm study in people with ROS1-positive advanced NSCLC. No participants were from the UK and only 7 were treatment naïve (46 had received previous chemotherapy). ROS1 mutation is rare. Therefore, additional data from trials of people with ALK-positive NSCLC (which is clinically similar to ROS1 mutation) were used by NICE to estimate the effect of crizotinib in TA529.

The matched-adjusted indirect comparison by Chu et al. 2020 and the simulated treatment comparison by Tremblay et al. 2022 used the same trials and found that

results of their analyses were affected by the small sample sizes, a low prevalence of ROS1-positive NSCLC, low event rates and consequent uncertainty reflected in wide confidence intervals. However, Tremblay et al. (2022) used more up-to-date PROFILE 1001 and entrectinib study data than used by Chu et al. (2020). Some outcomes were measured differently between the included studies.

There was relatively little data for crizotinib or entrectinib used as first line treatment, so the studies could not meaningfully match for this. Tremblay et al. (2022) did not adjust for the presence of CNS metastases due to the data not being collected at baseline in the PROFILE 1001 study, although Chu et al. (2020) did attempt to adjust for this using scenario analysis. Both studies were sponsored by the respective manufacturer of crizotinib and entrectinib.

The Tremblay et al. 2022 exploratory analysis comparing PROFILE 1001 with real world data reported a higher median overall survival in the clinical trial than the real-world population. However, following adjustment for sex, age, ECOG PS and smoking status, the results suggested that the real-world median overall survival was higher than in the clinical trial after accounting for differences in patient populations. This may suggest that the PROFILE 1001 clinical trial population is not fully reflective of the ROS1-positive NSCLC population seen in clinical practice.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Professional organisation submission

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.

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	Consultant Medical Oncologist/ [redacted]
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? Yes • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? Yes • Other (please specify):
5. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. Funded by registration fees and sponsorship
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes Sponsorship annual conference Belfast £22,000 + VAT
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	It has a similar mechanism of action, in that it inhibits the ROS1 kinase but it also inhibits other kinases such as ALK and MET which are responsible for some of its adverse events such as vision disturbance, pedal edema, bradycardia, and male hypogonadism. The comparator, entrectinib is a ROS1 kinase inhibitor but also targets different kinases, in addition, particularly NTRK1-3 kinases. This results in the different and perhaps more difficult adverse events to manage identified for entrectinib such as unsteadiness, vertigo, ataxia, neuropathy, pain on drug withdrawal, atypical fractures. Entrectinib seems to have more granular intracranial efficacy trial data than crizotinib: whether this reflects better intracranial activity over that observed for crizotinib remains debated. Crizotinib is a much more tolerable drug than entrectinib but at face value seems to have slightly less intracranial efficacy.
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	It is difficult to draw definitive comparisons between the two drugs on comparativeness, since ROS1+ NSCLC is such a rare disease, that there are no randomized data for comparisons, and only prospective single arm cohort/phase 2 data. On this basis, the impact of identifiable and non-identifiable prognostic covariates and selection criteria eg screening window, central biomarker testing requirements, and CNS eligibility criteria, differ between cohorts reported and mandate uncertainty in efficacy comparisons between the two drugs.
10. What impact would the technology have on the current pathway of care?	Crizotinib is a popular drug already used for ROS1+ NSCLC. It has a relatively straightforward toxicity profile and has good efficacy. Its relatively straightforward toxicity profile means that it can be used for patients where entrectinib is not tolerable and is often the preferred drug for elderly patients or for those in whom the CNS adverse events of entrectinib may not be feasible eg motorcyclists. It may be preferred over entrectinib in the absence of CNS involvement. Entrectinib is generally used for fit ECOG 0-1 patients, more so when the CNS is involved, but can be intolerable despite dose reduction due to CNS adverse events.
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	For use by oncologists in secondary care

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is currently used in clinical practice and would continue to be used in this way due to the lack of new evidence.
13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	No
14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Crizotinib is an important drug choice for ROS1+ patients and England oncologists. It is likely to offer similar efficacy benefits to entrectinib, but a different adverse event profile
15. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	No changes to current practice

17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	No new issues.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Crizotinib for treating ROS1-positive advanced non-small cell lung cancer (MA review of TA529) [ID6289]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 166086

Completed 16th July 2024

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Rebecca Harvey	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the review methods
Ashley Marsden	Critical appraisal of the company submission
Lynn Campbell	Clinical advice and critical appraisal of the clinical evidence

Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ALK	anaplastic lymphoma kinase
BID	twice daily
CDF	Cancer Drug Fund
CI	confidence interval
CNS	central nervous system
CS	company submission
CSR	Clinical Study Report
DCO	data cut-off
DoR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module
EAG	External Assessment Group
ERG	Evidence Review Group
ESS	effective sample size
GHS	global health status
HR	hazard ratio
HRQoL	health-related quality of life
IPD	individual patient data
ITC	indirect treatment comparison
K-M	Kaplan-Meier
MAIC	matching adjusted indirect comparison
NE	not estimable
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazards
ROS1	proto-oncogene tyrosine-protein kinase 1
SACT	Systemic Anti-Cancer Therapy
SLR	systematic literature review
STC	simulated treatment comparison
TRAE	treatment-related adverse event
TTE	time-to-event

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of the company cost comparison analysis. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Limitations of the crizotinib clinical effectiveness evidence	3.3 and 0
Issue 2	Limitations of the company ITCs (STCs and MAICs)	3.5
Issue 3	Company ITC results may not support carrying out a cost comparison analysis	4

ITC=indirect treatment comparison; MAICs=matching-adjusted indirect comparison; STC=simulated treatment comparison

1.2 Overview of the company cost comparison analysis

The company carried out a cost comparison analysis. The EAG considers that, if the NICE Appraisal Committee considers that crizotinib and entrectinib are similar and that, for decision making purposes, any differences in patient outcomes can be ignored, then the company cost comparison results are robust. The EAG has not generated any alternative cost comparison results.

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

Issue 1 Limitations of the crizotinib clinical effectiveness evidence

Report section	Section 3.3 and Section 0
Description of issue and why the EAG has identified it as important	• All the crizotinib effectiveness and safety data are derived from single-arm trials of patients with ROS1-positive advanced NSCLC. • It is likely that, if recommended by NICE, crizotinib will be used in the NHS in the first-line setting; however, none of the crizotinib trials and only 4/16 real-world crizotinib studies only included patients with previously untreated ROS1-positive advanced NSCLC. • Clinical advice to the EAG is that patients enrolled in the two main crizotinib trials (PROFILE 1001 trial and OxOnc trial) are broadly comparable to NHS patients with ROS1-positive advanced NSCLC, except for ethnicity; more PROFILE 1001 trial patients were Asian (39.6%) and all OxOnc trial patients were Asian. • SACT dataset and real-world study median OS varies substantially (21.9 months [SACT dataset] to 60 months [Zheng 2020]). • The difference between PROFILE 1001 trial and SACT dataset median OS results require further consideration by the company.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on how these issues might affect the generalisability of crizotinib clinical trial results to NHS patients.

EAG=External Assessment Group; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; OS=overall survival; ROS1=proto-oncogene tyrosine-protein kinase 1; SACT=systemic anti-cancer treatment

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

Issue 2 Limitations of the company ITCs (STCs and MAICs)

Report section	Section 3.5
Description of issue and why the EAG has identified it as important	**STCs** • The company did not present constant HR STCs. • The EAG considers that as STC 95% CIs reflect the amount of data available overall and do not reflect the number of patients providing data at each time point (which diminishes over time), it is not appropriate to infer lack of statistical significance (or claims of similarity) from the STC 95% CIs. • The company has presented STC average time-varying HRs. The EAG considers that it is not appropriate to average time-varying HRs and these average results should not be used to inform decision-making. **STCs and MAICs** • The company did not adjust for either line of treatment or brain metastases in the STCs or MAICs; the EAG considers that it was possible to adjust for line of treatment. • The PFS MAIC HR point estimate favours crizotinib, the OS MAIC HR point estimate favours entrectinib, and both CIs include 1; there is ongoing debate around whether CIs that include 1 should be used to support claims of similar health benefits.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not known
What additional evidence or analyses might help to resolve this key issue?	Constant HR STC results could be informative. ITC results adjusted for line of treatment could also be informative

CI=confidence interval; EAG=External Assessment Group; HR=hazard ratio; MAIC=matching-adjusted indirect comparison; OS=overall survival; PFS=progression-free survival; STC=simulated treatment comparison

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

Issue 3 Company ITC results may not support carrying out a cost comparison analysis

Report section	Section 4
Description of issue and why the EAG has identified it as important	None of the company STC or MAIC results statistically significantly favoured crizotinib over entrectinib. The company has assumed that as all the STC and MAIC results have wide CIs that include 1, this suggests that the efficacy of crizotinib and entrectinib are similar. However, rather than confirming similarity, the EAG considers that CIs describe the uncertainty inherent in the point estimate and indicate the range of values within which the reader can be reasonably sure that the true effect lies. The EAG, therefore, considers that the company ITC results have not conclusively demonstrated that the effectiveness of crizotinib is similar to the effectiveness of entrectinib; this means that it is not clear if a cost comparison approach is appropriate.
What alternative approach has the EAG suggested?	The EAG requested formal statistical testing to support the company's claim that crizotinib and entrectinib are similar in terms of efficacy and safety (clarification question A2)
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Conduct a non-inferiority test

CI=confidence interval; EAG=External Assessment Group; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; STC=simulated treatment comparison

1.6 Company cost comparison results

The EAG has not generated any alternative cost comparison results. Company cost comparison results are presented in Table B.

Table B Company base case results (total per person costs over a 20-year time horizon, PAS price for crizotinib and list price for entrectinib)

Treatment	Crizotinib	Entrectinib
Acquisition	[redacted]	£253,295
Administration	£899	£899
Monitoring	£12,263	£12,263
AE management	£81	£0
Total cost	[redacted]	**£266,457**
Incremental cost	-	[redacted]

AE=adverse event; CS=company submission; PAS=Patient Access Scheme
Source: CS, Table 28

The EAG's summary and critique of the company cost comparison analysis is presented in Section 4.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In 2018, a National Institute for Health and Care Excellence (NICE) Appraisal Committee (AC) reviewed the clinical and cost effectiveness of crizotinib (brand name: Xalkori) as a treatment option for adults with ROS proto-oncogene tyrosine-protein kinase 1 (ROS1)-positive advanced non-small cell lung cancer (NSCLC). In July 2018, NICE recommended crizotinib (TA529)[1] within the Cancer Drugs Fund (CDF) as a treatment option for adults with ROS1-positive advanced NSCLC, if the conditions set out in the Managed Access Agreement[2] (MAA) for crizotinib are followed. This appraisal is part of the CDF exit process and is a comparison of crizotinib versus entrectinib.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company in response to clarification questions.

2.2 Background

2.2.1 Non-small cell lung cancer

Lung cancer is made up of NSCLC, which accounts for around 80% to 85% of all lung cancer cases in England,[3] and small cell lung cancer. NSCLC is split into two main histological types: non-squamous type carcinomas and squamous type carcinomas.[4] Non-squamous type carcinomas represent around 70% of all NSCLC cases[5] and can be divided into two main histological subtypes: adenocarcinoma (40% of all lung cancer cases) and large cell carcinoma (10% to 15% of all lung cancer cases).[4]

Lung cancer is the second most common cancer in England; in 2021, 34,478 people were diagnosed.[6,7] Lung cancer is the most common cause of cancer-related death in England;[8] in 2017, the age standardised mortality rates were 58 per 100,000 for men and 43 per 100,000 for women.[9]

2.2.2 ROS1-positive NSCLC

NSCLC can be further classified by genetic markers that have been identified as oncogenic drivers. These include epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS1 rearrangements and rearranged during transfection (RET) fusions.[10] Patients with oncogene-driven NSCLC typically have just one genetic marker, as these mutations are typically mutually exclusive.[11] Patients with ROS1-positive NSCLC represent 1% to 2% of all NSCLC cases.[12]

2.2.3 Crizotinib

Crizotinib is a selective small-molecule inhibitor of the ROS1, ALK, Hepatocyte Growth Factor Receptor (HGFR) c-MET receptor tyrosine kinases. Crizotinib prevents the activation of downstream signalling pathways to stop tumour cell proliferation and to promote apoptosis.[13]

Crizotinib is administered orally and is available as 200mg and 250mg hard capsules.[14] The recommended dose for patients with ROS1-positive advanced NSCLC is 250mg twice daily (BID).[14] Dose reductions and dose interruptions are recommended based on an individual patient's safety and tolerability. If patients are unable to tolerate 250mg BID, it is recommended that the dose is reduced to 200mg BID and then, if required, to 250mg once daily. If patients are unable to tolerate 250mg once daily, it is recommended that crizotinib is discontinued.[14]

Crizotinib (200mg and 250mg hard capsules) has marketing authorisations from the European Medicines Agency (EMA)[15] and from the Medicines and Healthcare products Regulatory Agency (MHRA)[16,17] for adults with ROS1-positive NSCLC.

2.3 Company's overview of current service provision

The company has presented the current National Health Service (NHS) treatment pathway for patients with ROS1-positive advanced NSCLC and the positioning of crizotinib, should crizotinib be recommended by NICE for routine commissioning (CS, Figure 1). The treatment pathway was informed by the NICE lung cancer diagnosis and management guidelines (NG122),[10] which were updated in March 2024.

The company has positioned crizotinib as an alternative treatment to entrectinib for patients with ROS1-positive advanced NSCLC. The crizotinib marketing authorisation is for the treatment of adults with ROS1-positive advanced NSCLC.[14] Entrectinib is recommended by NICE as an option for treating ROS1-positive advanced NSCLC in adults who have not previously been treated with ROS1 inhibitors.[18]

Clinical advice to the EAG is that NHS patients who are suspected of having oncogene-driven NSCLC (i.e., typically, young, fit patients) would not start a treatment while waiting for gene sequencing results. Clinical advice to the EAG is that 90% to 95% of NHS patients with ROS1-positive advanced NSCLC are treated with crizotinib or entrectinib in the first-line setting and that approximately 5% to 10% of patients receive best supportive care. Clinical advice to the EAG is that patients would not be re-treated with a ROS1 inhibitor. Second-line or later treatment options following treatment with crizotinib or entrectinib in the first-line setting are the same for all patients (CS, Figure 1).

2.4 Critique of company's definition of decision problem

The key elements of the decision problem outlined in the final scope[19] issued by NICE and addressed by the company are summarised in Table 1. More information regarding the key issues relating to the decision problem is provided in Sections 2.4.3 to 2.4.7.

Table 1 Key elements of the decision problem

Parameter	Final scope[19] issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	Adults with ROS1-positive advanced NSCLC	Adults with ROS1-positive advanced NSCLC	None
Intervention	Crizotinib	Crizotinib 250mg	None
Comparator(s)	Entrectinib	Entrectinib	Clinical advice to the EAG is that entrectinib is the most relevant comparator.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse events of treatment • health-related quality of life	As per final scope: **Efficacy outcomes:** • overall survival • progression-free survival • response rates (overall response rate, partial response, duration of response, disease control rate) • time to tumour response • time-to-treatment failure • disease-free survival rate **Safety and tolerability outcomes:** • adverse events (any grade, serious adverse events, treatment-related) • treatment switch or discontinuation due to adverse events **Health-related quality of life:** Mean scores and change from baseline in patient reported outcome measures (EORTC QLQ-C-30, EORTC QLQ LC-13, EQ-5D)	Clinical advice to the EAG is that the company has presented results for the most relevant clinical outcomes. The company did not present any EQ-5D data.

Parameter	Final scope[19] issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost comparison has been carried out	The company has presented cost comparison analysis results over a 20-year time period. The EAG considers that the company ITC results have not conclusively demonstrated that the effectiveness of crizotinib is similar to the effectiveness of entrectinib. This means that it is not clear if a cost comparison approach is appropriate.
Special considerations including issues related to equity or equality	NA	NA	NA

EAG=External Assessment Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D=EuroQol-5 Dimensions; ITC=indirect treatment comparison; NA=not applicable; NICE=National Institute for Health and Care Excellence; NHS=National Health Service; NSCLC=non-small cell lung cancer; NA=not applicable; ROS1=proto-oncogene tyrosine-protein kinase 1

2.4.1 Main sources of crizotinib clinical trial evidence

The two main sources of crizotinib clinical effectiveness evidence are the PROFILE 1001[20] and OxOnc[21] trials. The PROFILE 1001[20] trial is a phase I, open-label, multi-centre (Australia, South Korea, USA) single-arm study; 53 patients provided efficacy and safety data (median follow-up was 62.6 months). The PROFILE 1001[20] trial enrolled seven patients with untreated disease and 46 patients who had received one or more prior chemotherapies.

The OxOnc[21] trial is a phase II, open-label, multi-centre (China, Japan, South Korea, Taiwan) single-arm study; 127 patients provided efficacy and safety data (median follow-up was 56.1 months). The OxOnc[21] trial enrolled 24 patients with untreated disease and 103 patients who had received one or more prior chemotherapies.

The company also provided supportive evidence from three single-arm trials (EUCROSS,[22] METROS,[23] and AcSé[24]), Systemic Anti-Cancer Therapy (SACT) data[25] and real-world evidence.[26-41]

Crizotinib evidence is only available from multiple non-randomised sources and sample sizes tend to be small. Overall, the data suggest that crizotinib is an effective treatment for patients with ROS1-positive advanced NSCLC; however, the EAG considers that it is not possible to draw firm conclusions about the relative effectiveness of crizotinib versus entrectinib.

2.4.2 Population

The PROFILE 1001[20] trial was conducted in centres in the Australia, South Korea and USA and the OxOnc[21] trial was conducted in Asia. Clinical advice to the EAG is that patients recruited to the PROFILE 1001[20] and OxOnc[21] trials are broadly comparable to NHS patients with ROS1-positive advanced NSCLC, except for ethnicity; more PROFILE 1001[20] trial patients were Asian (21/53, 39.6%) and all OxOnc[21] trial patients were Asian.

Neither the NICE guidance for crizotinib (TA529)[1] nor the NICE guidance for entrectinib (TA643)[18] stipulate line of treatment. However, the NICE lung cancer guidelines[42] treatment pathway diagram shows crizotinib and entrectinib positioned as first-line treatment options for patient with ROS1-positive NSCLC.

ROS1-positivity must be confirmed prior to initiation of treatment with crizotinib (or entrectinib) (CS, p11). Testing for ROS1-positivity, as described in the National Genomic Test Directory for Cancer[43] since 2019/2020, is standard practice in England.

2.4.3 Intervention

The intervention, crizotinib (250mg) is administered orally BID for as long as the disease responds or until unacceptable toxicity (CS, p82). Further details are provided in Section 2.2.3.

2.4.4 Comparators

Entrectinib is the only comparator listed in the final scope[19] issued by NICE. Entrectinib is recommended by NICE as an option for ROS1-positive advanced NSCLC in adults not previously treated with ROS1 inhibitors (TA643).[18] It is the only ROS1-targeted treatment for advanced NSCLC that is currently recommended by NICE. Clinical advice to the EAG is that entrectinib is the most relevant comparator to crizotinib.

Entrectinib is available as 100mg or 200mg capsules; the recommended dose of entrectinib is 600mg once daily.[44] It is recommended that patients are treated with entrectinib until disease progression or unacceptable toxicity.[44]

Central nervous system (CNS) metastases (including brain metastases) are common in advanced NSCLC and are a major clinical issue. Between 10% and 25% of patients have CNS metastases at the time of diagnosis, and up to 50% will develop them at some point during their disease.[45-48] CNS metastases are associated with a significant reduction in health-related quality of life (HRQoL) and estimated life expectancy.[49,50]

Clinical expert opinion sought by the Evidence Review Group (ERG) during TA643[51] supported the anticipated benefit of entrectinib on delaying CNS progression when compared with crizotinib; however, the ERG reported that there were few data to corroborate this CNS advantage over crizotinib and how this translates into overall disease progression and ultimately survival (TA643 ERG report,[51] p22). The EAG highlights that a randomised, phase III trial[52] to compare the efficacy and safety of entrectinib versus crizotinib in patients with advanced ROS1-positive NSCLC in patients with and without CNS metastases is ongoing.

2.4.5 Outcomes

There is no direct clinical effectiveness evidence for the comparison of crizotinib versus entrectinib. Clinical advice to the EAG is that the outcome data collected in the crizotinib and entrectinib single-arm trials are relevant to this appraisal and that the most relevant outcomes for patients with ROS1-positive advanced NSCLC have been presented by the company. The company carried out simulated treatment comparisons (STCs) and matching-adjusted indirect comparisons (MAICs) to compare the clinical effectiveness of crizotinib versus entrectinib for the key outcomes: progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and duration of response (DoR). The company indirect treatment comparisons

(ITCs) were populated with pooled entrectinib data from three single-arm trials (the ALKA-372-00, STARTRK-1[53] and STARTRK-2[54] trials); these data were sourced from a single publication.[55]

2.4.6 Economic analysis

The company has carried out a cost comparison analysis; costs were assessed over 20 years. Crizotinib and entrectinib are available to the NHS at confidential Patient Access Scheme (PAS) prices. The confidential price of entrectinib is not known to the company. Cost effectiveness results generated using the discounted prices for both drugs are presented in a confidential appendix.

Appropriateness of a cost comparison analysis

The EAG considers that the company ITC results do not provide sufficiently robust evidence to demonstrate that, compared to entrectinib, crizotinib provides similar or greater health benefits; therefore, it is not clear whether a cost comparison approach is appropriate.

2.4.7 Subgroups

No subgroups were specified in the final scope[19] issued by NICE; however, the company provided (CS, Appendix E.1.1) ORR, PFS and OS subgroup results stratified by:

- presence of brain metastases at baseline (data were available from the OxOnc[21] and EUCROSS[22] trials only)
- number of prior lines of treatment for advanced NSCLC
- Asian ethnicity (data were available from the PROFILE 1001[20] trial only).

Subgroup populations were small and results are uncertain (wide confidence intervals [CIs]).

2.4.8 Other considerations

None.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support the use of crizotinib as a treatment option for patients with ROS1-positive advanced NSCLC.

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify and select crizotinib and entrectinib clinical effectiveness evidence for patients with ROS1-positive advanced NSCLC. Full details of the company's methods are presented in the CS (Appendix D). The company's literature searches were comprehensive and were completed within 12 months of the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 2. The EAG considers that the company's systematic review methods were appropriate.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1, p6 and CS, Appendix D.1.3, Table 4.
Were appropriate sources searched?	Yes	See CS, Appendix D.1.1, pp6 to 7.
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D.1.1 and D.1.2.
Were appropriate search terms used?	Yes	See CS, Appendix D.1.2, Table 1 to Table 3.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.3, Table 4.
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D.1.3, p10.
Were data extracted by two or more reviewers independently?	Yes	See company response to clarification question C2. One reviewer extracted data and the data were then checked by a second (independent) reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See company response to clarification question C3. The company quality assessed the PROFILE 1001,[20] OxOnc,[56] METROS,[23] EUCROSS,[22] AcSé[24] and STARTRK-2[54] trials using the ROBINS-I tool[57] (CS, Section 3.6). The EAG considers that it was not appropriate to use the ROBINS-I tool[57] as this tool is only relevant for studies of ≥2 treatment groups. In response to clarification question C3, the company quality assessed these trials[20,23,24,54,56,58] using the CASP checklist[59] for cohort studies (see Appendix 1, Section 6.1, Table 25).
Was the quality assessment conducted by two or more reviewers independently?	Unclear	See CS, Appendix D.1.3, p11. "After completion of the full-text review, 100% of the screened articles were quality checked by a third independent reviewer, and the final list of included studies was compiled." The EAG considers that it is unclear whether study selection was "quality checked" or whether the company is referring to quality assessment. The EAG considers that included studies should be quality assessed by two independent reviewers.
Were attempts to synthesise evidence appropriate?	Yes	ITCs were performed. See Section 3.5.3 for the company's methods and the EAG's critique of the indirect evidence syntheses.

CASP=Critical Appraisal Skills Programme; CS=company submission; EAG=External Assessment Group; ITCs=indirect treatment comparisons; ROBINS-I=Risk Of Bias In Non-randomized Studies of Interventions
Source: EAG in-house checklist

3.2 Critique of main trials of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

The company SLR identified the following studies:

- five trials that included crizotinib (the PROFILE 1001,[20] OxOnc,[21] EUCROSS,[22] METROS[23] and AcSé[24] trials)
- two trials that included entrectinib (the STARTRK-2[54] and B-FAST[60] trials)
- a pooled analysis[55] of three entrectinib trials (the ALK-372-001, STARTRK-1[53] and STARTRK-2[54] trials).

The PROFILE 1001[20] and OxOnc[21] crizotinib trials provided data that were used in the company ITCs, whilst the EUCROSS[22] trial provides crizotinib CNS subgroup analysis results; the EAG has focused on these three crizotinib trials (Section 3.2.2 to Section 3.2.5). Information relating to the METROS[23] and AcSé[24] crizotinib trials can be found in the CS (CS, Table 7 [key characteristics], Table 8 [baseline characteristics], Table 11 and Table 12 [trial results]).

A full description and critique of the indirect trial evidence is presented in Section 3.5.1 to Section 3.5.5.

3.2.2 Characteristics of the PROFILE 1001, OxOnc and EUCROSS trials

The key characteristics of the PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials are presented in Table 3. Key PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trial eligibility criteria were similar.

Table 3 Key characteristics of the PROFILE 1001, OxOnc and EUCROSS trials

Trial parameter	PROFILE 1001[20] trial (N=53)	OxOnc[21] trial (N=127)	EUCROSS[22] trial (N=34)
Design	• Phase I, multi-centre, international (Australia, South Korea and USA), open-label, single-arm trial • 2006 to 2020	• Phase II, open-label, multi-centre, international (China, Japan, South Korea and Taiwan), single-arm trial • 2013 to 2016	• Phase II, open-label, multi-centre, international (Germany, Spain and Switzerland), single-arm trial • 2014 to 2020
Population	• Patients (≥18 years) with histologically confirmed ROS1-positive advanced NSCLC • ECOG PS 0 to 1 (patients with ECOG PS 2 could enter trial if agreed by the investigator and sponsor) • Any number of prior systemic therapies permitted • Patients with brain metastases were eligible if asymptomatic or neurologically stable for ≥4 weeks if treated	• Patients (≥18 years) with histologically or cytologically confirmed ROS1-positive advanced NSCLC (and negative for ALK-rearrangements) • ECOG PS 0 to 1 • ≤3 prior systemic therapies for advanced NSCLC • Patients with brain metastases were eligible if asymptomatic or neurologically stable for ≥2 weeks if treated	• Patients (>18 years) with ROS1-positive advanced NSCLC confirmed by central FISH testing • Adenocarcinoma • ECOG PS 0 to 2 • Any number of prior systemic therapies permitted (no prior ALK/ROS1 inhibitor) • Life expectancy ≥12 weeks • Patients with brain metastases were eligible if asymptomatic and not requiring increasing doses of steroids
Intervention	• 250mg BID oral crizotinib	• 250mg BID oral crizotinib	• 250mg BID oral crizotinib
Primary outcome	• ORR by investigator assessment	• ORR by independent radiology review	• ORR by local assessment
Secondary outcomes	• OS, PFS, TTF and safety	• PFS, OS, DoR, time to first tumour response, DCR, QoL and safety	• DCR, PFS, DoR, OS and safety
Data cut-off presented in CS	• 30 June 2018	• 30 July 2016 • 1 July 2020 (OS only)	• 3 April 2017[a]

[a] OS data from Michels 2022[61] were presented in the CS but the data cut-off date was not reported
[b] The EAG identified and extracted data from a more recent EUCROSS trial publication (Michels 2024;[22] March 2022 DCO)
ALK=anaplastic lymphoma kinase; BID=twice daily; CS=company submission; DCO=data cut-off; DCR=disease control rate; DoR=duration of response; EAG=External Assessment Group; ECOG PS=Eastern Cooperative Oncology Group performance status; FISH=fluorescence in situ hybridization; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life; ROS1=proto-oncogene tyrosine-protein kinase 1; TTF=time to treatment failure
Source: CS, Table 7 and CS, Appendix D.1.4, Table 8

3.2.3 Characteristics of PROFILE 1001, OxOnc and EUCROSS trial patients

The baseline characteristics of the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial patients are presented in Table 4.

Only a small proportion of PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial patients (13.2%, 18.9% and 20.6%, respectively) were treated with crizotinib in the first-line setting.

Clinical advice to the EAG is that, with the exception of ethnicity, PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial patient characteristics are similar to the characteristics of NHS patients with ROS1-positive advanced NSCLC. Clinical advice to the EAG is that, compared with NHS patients, more PROFILE 1001[20] trial patients (21/53, 39.6%) were Asian; all OxOnc[21] trial patients were Asian (all EUCROSS[58] trial patients were European).

In the TA529 CS,[62] the company considered that OxOnc[21] trial results were not generalisable to NHS patients because the study only included East-Asian patients and did not present OxOnc[21] trial results. However, in the CS, the company has presented the OxOnc[21] trial as one of the main sources of clinical effectiveness evidence.

Clinical advice to the EAG is that the presence of brain metastases at baseline is an important prognostic factor; the proportion of PROFILE 1001[20] trial patients with brain metastases at baseline was not reported. Clinical advice to the EAG is that patients with ROS1-positive NSCLC may develop brain metastases; patients with brain metastases may have worse outcomes, including worse HRQoL, than patients without brain metastases.

Table 4 Baseline characteristics of crizotinib trial patients

Characteristic	Crizotinib		
	PROFILE 1001[20] trial (N=53)	OxOnc[21] trial (N=127)	EUCROSS[22] trial (N=34)
Age, median (range), years	55 (25 to 81)	51.5 (22.8 to 79.7)	56 (33 to 84)
Male, n (%)	23 (43.4)	54 (42.5)	15 (44.1)
Ethnicity, n (%)			
White	30 (56.6)	0 (0)	31 (91.2)
Asian	21 (39.6)	127 (100)	2 (5.9)
Black	2 (3.8)	0 (0)	0 (0)
Other/unknown	0 (0)	0 (0)	1 (2.9)
Not reported	0 (0)	0 (0)	0 (0)
Previous lines of treatment, n (%)			
0	7 (13.2)	24 (18.9)	7 (20.6)
1	22 (41.5)	53 (41.7)	12 (35.3)
2	12 (22.6)	31 (24.4)	5 (14.7)
≥3	12 (22.6)	19 (15.0)	10 (29.4)
ECOG PS, n (%)			
0	23 (43.4)	34 (26.8)	12 (35.3)
1	29 (54.7)	93 (73.2)	20 (58.8)
2	1 (1.9)	0 (0)	2 (5.9)
Brain metastases, n (%)	NR	[redacted] [a]	7 (20.6) [b]
Smoking status, n (%)			
Never smoked	40 (75.5)	91 (71.7)	23 (67.6)
Previous smoker	13 (24.5)	36 (28.3)	11 (32.4)
Current smoker	0 (0)		0 (0)

[a] In response to clarification question A5, the company reported that [redacted] ([redacted]) OxOnc[21] trial patients had brain metastases at baseline
[b] One EUCROSS[22] trial patient had unknown brain metastases status at baseline
CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; NR=not reported
Source: CS, Table 8 and company response to clarification question A5

3.2.4 Quality assessment of the PROFILE 1001, OxOnc and EUCROSS trials

In response to clarification question C3, the company conducted a quality assessment of the PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials using the Critical Appraisal Skills Programme (CASP) checklist[59] for cohort studies. The company's assessments and EAG comments are presented in Appendix 1, Section 6.1, Table 25. The EAG assessment is that PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials are of good methodological quality; however, the EAG cautions that results from single-arm trials may be subject to bias.

3.2.5 Summary of statistical analyses: PROFILE 1001 and OxOnc trial

The company has presented summaries of the statistical analyses adopted for the PROFILE 1001[20] and OxOnc[21] trials (CS, Table 9). The company also provided the PROFILE 1001 trial Clinical Study Report[63] (CSR), PROFILE 1001 trial protocol,[64] the OxOnc CSR[65] and OxOnc trial protocol.[66] A summary of statistical analyses is presented in Table 5. The EAG considers that, based on the information available, appropriate statistical approaches were adopted.

Table 5 Summary of statistical analyses

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PROFILE 1001[20] (NCT00585195)	Null hypothesis (H_0): The rate of response to crizotinib would be 10% or less. Alternative hypothesis (H_A): The rate of response rate to crizotinib would be more than 10%. The primary endpoint was the ORR.	K-M analysis of time-to-event data to estimate median event times and the Brookmeyer–Crowley method to calculate two-sided 95% CI. All analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute).	It was initially determined that 30 patients were needed to achieve a power of at least 85% to test the null hypothesis at a one-sided alpha level of 0.05 with the use of a single-stage design. For the alternative hypothesis, the response rate was assumed to be 30%. As of April 2012, there were eight responses (among 14 patients who could be evaluated), which exceeded the six responses required to reject the null hypothesis. To permit a more accurate assessment of the efficacy and safety of crizotinib in this population, we expanded the sample size to a maximum of 50 patients.	The ORR was similar for the first 30 patients who were enrolled (67%) and the additional 20 patients who were enrolled (80%). Patients completing: 49/50 (98%). No information about management of patient withdrawals.
OxOnc[21] (NCT01945021)	Null hypothesis (H_0): NR Alternative hypothesis (H_A): NR The primary endpoint was ORR by independent radiology review.	The ORR (percentage of patients with a best overall response of a confirmed CR or confirmed PR) and DCR (percentage of patients with a confirmed CR or confirmed PR or SD) by IRR were evaluated in the response-evaluable population, and the 95% CIs were calculated using the exact method on the basis of the F-distribution. DoR was summarised by K-M method and descriptive statistics; TTR was summarised using descriptive statistics only. DoR and TTR were assessed only in the subgroup of responder-patients in the response-evaluable population.	The safety analysis population included all enrolled patients who received at least one dose of crizotinib; the response-evaluable population was defined as all patients in the safety analysis population who had an adequate baseline tumour assessment. An ORR of 30% was considered a clinically meaningful threshold for this study, and a lower limit of the two-sided 95% CI around the observed ORR greater than this threshold would demonstrate the efficacy of crizotinib. By assuming a 50% true ORR, the statistical power to demonstrate efficacy on the basis of this threshold was 98.2% with 100 evaluable patients; the 95% CI for an observed ORR of 50% is 40% to 60%. A total of 110 patients were projected to be enrolled.	Patients completing: 126/127 (99%). At the DCO, median duration of crizotinib treatment was 18.4 months (range, 0.1–34.1 months), and 63 patients (49.6%) were still receiving crizotinib. No information about management of patient withdrawals.

Study name (Study number)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		In the safety analysis population, the K-M method was used to estimate median PFS and OS; two-sided 95% CIs are provided. PRO end points were analysed in the PRO-evaluable population (all patients in the safety analysis population who completed a baseline and one or more post–baseline PRO assessments). Changes in EORTC QLQ-C30 and EORTC QLQ-LC13 scores of ≥10 points from baseline were considered clinically meaningful and statistically significant if the 95% CIs did not include 0.		

CI=confidence interval; CR=complete response; CS=company submission; DCO=data cut-off; DCR=disease control rate; DoR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; IRR=independent radiology review; K-M=Kaplan-Meier; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; PRO=patient-reported outcome; SD=stable disease; TTR=time to tumour response
Source: CS, Table 9

3.3 PROFILE 1001, OxOnc and EUCROSS trial clinical efficacy results

Key PROFILE 1001[20] (N=53), OxOnc[21] (N=127) and EUCROSS[58] (N=34) trial results are presented in Section 3.3.1 to Section 3.3.3. Due to protocol violations (n=4), results from 30/34 EUCROSS[58] trial patients are available. PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial median PFS and OS follow-up data are provided in Table 6.

Table 6 PROFILE 1001, OxOnc and EUCROSS trial key survival results

	PROFILE 1001[20] trial[a] (N=53)	**OxOnc[21] trial[b] (N=127)**	**EUCROSS[22] trial[c] (N=30)**
Median PFS follow-up, months (95% CI)	59.6 (42.4 to 66.4)	21.3 (18.7 to 21.5)	41.1 (34.9 to NE)
Median OS follow-up, months (95% CI)	62.6 (58.2 to 66.6)	56.1 (52.1 to 59.4)	81.4 (78.7 to 87.2)

[a] PROFILE 1001[20] trial PFS and OS data were extracted from Shaw 2019[20] (30 June 2018 DCO)
[b] OxOnc trial PFS data and OS data were extracted from Wu 2018[56] (30 July 2016 DCO) and Wu 2022[21] (1 July 2020 DCO), respectively
[c] EUCROSS trial PFS and OS data were extracted from Michels 2024[22] (March 2022 DCO)
CI=confidence interval; CS=company submission; DCO=data cut-off; NE=not estimable; NR=not reported; OS=overall survival; PFS=progression-free survival
Source: CS, Table 11; Company response to clarification question A6; Shaw 2019;[20] Wu 2018;[56] Wu 2022;[21] Michels 2024[22]

3.3.1 Objective response rate

ORR was the primary outcome in the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trials; ORRs are presented in Table 7. ORRs were consistent across trials, however, no EUCROSS[58] trial patients achieved a complete response. Duration of response (DoR) was longest in the PROFILE 1001[20] trial. Time to tumour response (TTR) was very similar in the PROFILE 1001[20] and OxOnc[56] trials.

Table 7 PROFILE 1001, OxOnc and EUCROSS trial ORR results

Outcome	PROFILE 1001[20] trial[a] (N=53)	OxOnc[56] trial[b] (N=127)	EUCROSS[58] trial[a,c] (N=30)
ORR, n (%) (95% CI)	38 (72) (58 to 83)	91 (71.7) (63.0 to 79.3)	21 (70.0) (50.6 to 85.3)
CR, n (%)	6 (11.3)	17 (13.4)	0 (0.0)
PR, n (%)	32 (60.4)	74 (58.3)	21 (70.0)
SD, n (%)	10 (18.9)	21 (16.5)	6 (20.0)
PD, n (%)	3 (6)	9 (7.1)	2 (6.7)
DCR, n (%) (95% CI)	48 (90.6) (NR)[d]	Week 8: 112 (88.2) (81.3 to 93.2) Week 16: 102 (80.3) (72.3 to 86.8)	27 (90.0) (73.5 to 97.9)
Median DoR, months (95% CI)	24.7 (15.2 to 45.3)	19.7 (14.1 to NE)	19.0 (9.1 to NE)
Median TTR, months (range)	1.8 (1.0 to 23.8)[e]	1.9 (1.6 to 15.8)	Not measured

[a] Investigator-assessed
[b] By independent radiology review
[c] Response-evaluable patients (N=30)
[d] The company calculated the PROFILE 1001[20] trial DCR by adding the PR, CR and SD rates
[e] PROFILE 1001[20] trial median TTR was reported in weeks, the EAG converted to months by dividing by 4.345
CI=confidence interval; CR=complete response; CS=company submission; DCR=disease control rate; DoR=duration of response; NE=not estimable; NR=not reported; ORR=objective response rate; PD=progressed disease; PR=partial response; SD=stable disease; TTR=time to tumour response
Source: CS, Table 12; Shaw 2019;[20] Wu 2018;[56] Michels 2019[58]

3.3.2 PFS and OS results

Crizotinib PFS and OS results are presented in Table 8. The EAG identified and extracted EUCROSS trial[22] PFS and OS data from the most up to date published data (data cut-off [DCO] March 2022) presented in Michels 2024.[22]

Table 8 PROFILE 1001, OxOnc and EUCROSS trial PFS and OS results

Outcome	PROFILE 1001[20] trial[a] (N=53)	OxOnc[21,56] trial[b] (N=127)	EUCROSS[22] trial[a] (N=30)[c]
Median PFS, months (95% CI)	19.3 (15.2 to 39.1)	15.9 (12.9 to 24.0)	19.4 (10.1 to 32.2)
Median OS, months (95% CI)	51.4 (29.3 to NE)	44.2 (32.0 to NE)[d]	54.8 (17.1 to NE)

[a] Investigator-assessed
[b] By independent radiology review
[c] Response-evaluable patients (N=30)
CI=confidence interval; CS=company submission; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: CS, Table 11; Shaw 2019;[20] Wu 2018;[56] Wu 2022;[21] Michels 2024[22]

3.3.3 Subgroup analyses

No subgroups were specified in the final scope[19] issued by NICE. However, the company provided (CS, Section 3.8 and Appendix E) PROFILE 1001, [20] OxOnc[21] and EUCROSS[22] trial ORR, OS and PFS results, including:

- presence of brain metastases at baseline (CS, Appendix E.1.1 and company response to clarification question A5, Table 5; data were available from the OxOnc[21] and EUCROSS[22] trials only)
- number of prior lines of treatment for advanced NSCLC (CS, Appendix E.1.2 and company response to clarification question A4, Table 3)
- Asian ethnicity (CS, Appendix E.1.2, Table 31; data were only available from the PROFILE 1001[20] trial)

Presence of brain metastases at baseline (Yes/No)

The presence of brain metastases at baseline was assessed in the OxOnc[21] trial and the EUCROSS[58] trial. Subgroup populations were small, particularly the EUCROSS[22] trial baseline brain metastases subgroup (n=6), and results are uncertain (wide CIs).

Unusually, in the OxOnc[56] trial, ORRs were higher in the subgroup with brain metastases than in the subgroup without brain metastases; in the EUCROSS[58] trial, ORRs were similar in the subgroups with and without brain metastases (Table 9).

Median OS and median PFS were shorter in the subgroups with brain metastases than in the subgroups without brain metastases (Table 10).

Table 9 ORR subgroup analyses results stratified by presence of baseline brain metastases

OxOnc[21] trial				EUCROSS[58] trial[a,b,c]			
Brain metastases (n=15)		No brain metastases (n=112)		Brain metastases (n=6)		No brain metastases (n=23)	
ORR, n/N	% (95% CI)	ORR, n/N	% (95% CI)	ORR, n/N	% (95% CI)	ORR, n/N	% (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]	4/6	66.7 (22.3 to 95.7)	16/23	69.6 (47.1 to 86.8)

[a] Investigator-assessed ORR
[b] Fisher exact for presence of baseline brain metastases (Yes vs No); p=1.0
[c] One patient had unknown brain metastases status at baseline
CI=confidence intervals; ORR=objective response rate
Source: Company response to clarification question A5; Michels 2019[58]

Table 10 OS and PFS subgroup analyses results stratified by presence of baseline brain metastases

	OxOnc[21] trial		EUCROSS[22] trial[a,b]	
	Brain metastases (n=15)	**No brain metastases (n=112)**	**Brain metastases (n=6)**	**No brain metastases (n=23)**
Median PFS, months (95% CI)	[redacted]	[redacted]	9.4 (6.9 to NE)	23.7 (10.5 to NE)
			HR=1.8 (0.65 to 5.0), p=0.237	
Median OS, months (95% CI)	[redacted]	[redacted]	13 (1.7 to NE)	NE (21.6 to NE)
			HR=2.3 (0.81 to 5.5), p=0.117	

[a] Investigator-assessed PFS
[b] OxOnc trial median OS were only reported for the ITT population (N=34)
CI=confidence intervals; HR=hazard ratio; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Company response to clarification question A5; Michels 2024[22]

Number of prior lines of treatment for advanced NSCLC

Subgroup analysis results stratified by prior lines of treatment for advanced NSCLC (0 versus ≥1) were available from the PROFILE 1001[20] and OxOnc[21] trials; EUCROSS[22] trial subgroup analyses were stratified by 0 to 1 versus ≥2 prior lines of treatment. Subgroup populations were all small (n<17) and results are uncertain (wide confidence intervals).

The PROFILE 1001[20] and OxOnc[21] trial subgroup results suggested that patients with previously untreated NSCLC may achieve higher ORRs; however, in the EUCROSS[22] trial, line of treatment appeared to have no impact on ORRs (Table 11).

The OxOnc[21] trial subgroup results suggested that patients with previously untreated NSCLC had a longer median PFS and a longer median OS than patients who had received ≥1 prior lines of treatment; however, EUCROSS[22] trial subgroup results suggest that patients who had received 0 to 1 prior lines of treatment had shorter median PFS than patients who had ≥2 prior lines of treatment (Table 12).

Table 11 ORR subgroup results stratified by number of prior lines of treatment for advanced NSCLC

Number of prior LOTs		**PROFILE 1001[20] trial[a]**		**OxOnc[21] trial**		**EUCROSS[58] trial[a,b]**	
		0	**≥1**	**0**	**≥1**	**0 to 1**	**≥2**
ORR	n/N	6/7	32/46	18/24	73/103	11/16	10/14
	% (95% CI)	85.7 (42.1 to 99.6)	69.6 (54.2 to 82.3)[c]	[redacted]	[redacted]	68.8 (41.3 to 89.0)	71.4 (41.9 to 91.6)

[a] Investigator-assessed ORR
[b] Fisher exact for 0 to 1 prior lines of treatment versus ≥2 prior lines of treatment; p=1.0
[c] In response to clarification question A4, the company reported that the PROFILE 1001 trial ORR subgroup result for patients who had received ≥1 prior lines of treatment was [redacted]
CI=confidence intervals; LOT=line of treatment; ORR=objective response rate
Source: Company response to clarification question A4, Table 3; Michels 2019[58]

Table 12 OS and PFS subgroup analyses results stratified by number of prior lines of treatment for advanced NSCLC

Number of prior LOTs	PROFILE 1001[20] trial		OxOnc[21] trial		EUCROSS[58] trial[a]	
	0 (n=7)	≥1 (n=46)	0 (n=[redacted])	≥1 (n=[redacted])	0 to 1 (n=16)	≥2 (n=14)
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	17.8 (7.0 to NE)	20.0 (6.9 to NE)
	NA		NA		HR=0.833 (0.328 to 2.37), p=0.805	
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	NE (16.4 to NE)	NE (13.0 to NE)
	NA		NA		HR=1.27 (0.34 to 4.73), p=0.7234	

[a] Investigator-assessed ORR
CI=confidence intervals; CS=company submission; HR=hazard ratio; LOT=line of treatment; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Company response to clarification question A4, Table 3; Michels 2019[58]

Ethnicity

The company presented (CS, Appendix E.1.2, Table 31) PROFILE 1001[20] trial ORR subgroup results (Asian versus non-Asian); ORRs were similar for Asian (n=15/21, 71.4%, 95% CI: 47.8% to 88.7%) and non-Asian patients (n=23/32, 71.9%, 95% CI: 53.3% to 86.3%).[20] The company did not report OS or PFS subgroup analysis results stratified by ethnicity.

3.4 Real-world evidence

The company has presented real-world evidence (CS, Section 3.10) for crizotinib as a treatment for ROS1-positive advanced NSCLC from a National Disease Registration Service (NDRS) report of SACT data[25] and from 16 real-world studies.[26-41] The company did not provide details of how the real-world studies were identified.

3.4.1 SACT dataset

The SACT report[25] includes data from 163 patients who had received crizotinib via the CDF. Data were collected between 31 May 2018 and 30 June 2023.

Baseline characteristics: SACT data versus clinical trial data

The company presented (CS, Table 16) a summary of the baseline characteristics of SACT dataset[25] patients. The EAG has compared the baseline characteristics of SACT dataset[25] patients with the baseline characteristics of PROFILE 1001,[20] OxOnc[21] and EUCROSS trial patients (Table 4):

- SACT dataset[25] patients were on average older (median age: 63 years) than PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trial patients (median age: 55 years, 51.5 years and 56 years, respectively)

- the SACT dataset[25] included a higher proportion of patients with previously untreated advanced NSCLC (121/163, 74.2%) than the PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials (13%, 18.9% and 21%, respectively)
- the SACT dataset[25] included a smaller proportion of patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 (120/163, 73.6%) than the PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials (98.1%, 100.0% and 94.1%, respectively).

At the time of data cutoff, 77% of SACT dataset[25] patients (126/163) were no longer on treatment and, of these, 35% (45/126) had died.

Efficacy results: SACT data versus clinical trial data

The only available SACT dataset[25] efficacy outcome was OS (CS, Table 17); median follow-up was 17.4 months. Median OS was shorter in the SACT dataset[25] (21.9 months, 95% CI: 17.7 to 29) than in the PROFILE 1001[20] (51.4 months, 95% CI: 29.3 to not estimable [NE]), xOnc[21] (44.2 months, 95% CI: 32.0 to NE) and EUCROSS[22] trials (54.8 months, 95% CI: 17.1 to NE). The EAG highlights that there is a large difference in median OS between the SACT dataset and the PROFILE 1001[207] (difference: 29.5 months), OxOnc[21] (difference: 22.3 months) and EUCROSS[22] trials (difference: 32.9 months).

The EAG notes that SACT dataset[25] patients were older and less fit than patients in the PROFILE 1001[20] trial. In addition, compared with the than in the PROFILE 1001[20] trial (13%), more patients in the SACT dataset[25] (64%) had previously untreated NSCLC. It is not clear how these differences may have affected median OS results. In response to clarification question A3, the company reported that, collectively, evidence from two clinical trials[21,22] and three retrospective studies[27,28,33] did not provide evidence that, compared to those receiving crizotinib in the first-line setting, crizotinib was less efficacious in pretreated patients. The EAG considers that the company has not provided a plausible explanation for differences between SACT dataset and PROFILE 1001[20] trial median OS results. The magnitude of difference between the SACT dataset[25] and PROFILE 1001[20] trial median OS results requires further consideration by the company.

3.4.2 Real-world studies

All 16 real-world studies[26-41] were retrospective studies. Most (12/16) of the real-world studies[27,28,30-36,38,39,41] were conducted in Asia, two real-world studies[37,40] were conducted in the USA and two real-world studies[26,29] were conducted in Europe (but not in the UK).

Most (9/16) of the real-world studies[26,30-33,37-39,41] enrolled <30 patients; one real-world study[35] included 168 patients. Most (11/16) of the real-world studies[26-29,31,33,37-41] included patients who received crizotinib regardless of number of prior lines of treatment, although four real-world

studies[30,34-36] only included patients with previously untreated NSCLC and one real-world study[32] only included patients who received crizotinib as a second- or later-line treatment.

Baseline patient characteristics: real-world study data versus clinical trial data

The EAG has compared real-world study[26-41] baseline patient characteristics (CS, Table 16) with the baseline characteristics of PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial patients (data presented in Table 4). The EAG considers that the real-world study[26-41] and clinical trial[20-22] baseline patient characteristics are broadly consistent, with five exceptions. Compared to the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trials:

- two real-world studies[26,35] included a higher proportion of male patients
- two real-world studies[37,40] populations included a higher proportion of White patients
- six real-world studies[27,28,31,37,40,41] included a higher proportion of patients who were treated with crizotinib in the first-line setting; four real-world studies[30,34-36] only included patients who were treated with crizotinib in the first-line setting
- three real-world studies[35,39,40] included a higher proportion of patients with baseline brain metastases
- one real-world study included a smaller proportion of patients who were never smokers.

Efficacy results: real-world study data versus clinical trial data

ORR results and key survival results from the real-world studies are presented in the CS (Table 17). ORR results are available from 14/16 real-world studies.[26-36,38,39,41] Compared to PROFILE 1001[20] (71.7%), OxOnc[56] (71.7%) and EUCROSS[58] (70.0%) trial ORR results, ORRs were higher in 9/16 real-world studies[27,29-32,34,35,38,39] (80.0% to 93.8) and were lower in four real-world studies[26,33,36,41] (56.6% to 64.7%). Consistent with the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial results, in the real-world studies[26-36,38,39,41] some patients achieved a complete response (0.0% to 25.0%), most patients achieved a partial response (37.5% to 89.5%) and a small proportion of patients achieved stable disease (5.3% to 29.4%).

Median follow-up was reported by 10/16 real-world studies[26,27,30,34-40] (CS, Table 17: 11.1 months to 38.4 months) and was shorter than the reported PROFILE 1001,[20] OxOnc,[21] and EUCROSS[61] trial median follow-up (CS, Table 11: 62.6 months, 56.1 months and 81.4 months, respectively).

Median OS was reported by 11/16 real-world studies.[26-28,30,34,37-41] Median OS was not reached in 5/16 real-world studies.[26,30,34,38,41] Compared to the PROFILE 1001,[20] OxOnc[21] and EUCROSS trial median OS results (51.4 months, 44.2 months and 54.8 months, respectively), median OS was shorter in five real-world studies,[27,28,37,39,40] (range: 27.3 months[40] to 41 months[28]) and was longer in one real-world study[35] (60 months).

Median PFS was reported by 14/16 real-world studies.[27-39,41] Median PFS was not reached in two real-world studies.[38,41] Median PFS varied across the real-world studies and ranged from 9.1 months[29] to 23 months[35].

The EAG considers that it is difficult to draw firm conclusions about the efficacy of crizotinib from the real-world study results due to study heterogeneity and because not all studies reported all outcomes of interest.

Real-world study subgroup analyses

The Zhang 2021,[35] Xu 2020[34] and Zheng 2020[36] real-world studies reported subgroup analysis results stratified by presence of brain metastases at baseline (Table 13):

- in the Zhang 2021 study,[35] ORR was numerically lower in patients with brain metastases than in patients without brain metastases
- in the Zhang 2021,[35] Xu 2020[34] and Zheng 2020[36] studies, median PFS was shorter in patients with brain metastases than in patients without brain metastases (in the Zhang 2021[35] study, the difference in PFS between subgroups was statistically significant)
- in the Zheng 2020 study,[36] median OS was numerically shorter in patients with brain metastases than in patients without brain metastases.

Table 13 Real-world studies ORR, OS and PFS subgroup analyses results stratified by baseline brain metastases

	Zhang 2021[35] study		Xu 2020[34] study		Zheng 2020[36] study	
	Brain metastases (n=45)	No brain metastases (n=123)	Brain metastases (n=11)	No brain metastases (n=45)	Brain metastases (n=11)	No brain metastases (n=18)
ORR, n (%)	34 (77.8)	108 (87.8)	NR	NR	NR	NR
	p=0.642		NR		NR	
Median PFS, months (95% CI)	16.0 (NR)	22.0 (NR)	12.0 (NR)	15.0 (NR)	12.0 (10.1 to 13.9)	24.0 (1.0 to 47.0)
	p=0.03		p=0.249		p=0.462	
Median OS, months (95% CI)	NR	NR	NR	NR	50.0 (4.6 to 95.4)	60.0 (NE to NE)
	NR		NR		p=0.533	

CI=confidence intervals; CS=company submission; NE=not estimable; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Source: CS, Appendix E.1.2, Table 32

3.4.3 Conclusions: SACT and real-world evidence

SACT dataset[25] and real-world study[26-41] results have been sourced from non-randomised, single-arm retrospective studies (mostly small sample size). SACT dataset and real-world study median OS varied substantially (21.9 months [SACT dataset[25]] to 60 months [Zheng 2020[36]]).

3.5 EAG summary and critique of the indirect comparisons

The only comparator listed in the final scope[19] issued by NICE was entrectinib. As the company's SLR did not identify any head-to-head trials investigating the efficacy of crizotinib versus entrectinib, the company conducted ITCs to estimate comparative efficacy. Results from a series of ITCs are presented in the CS (Section B.3.12 and Appendix D).

3.5.1 Summary of company's ITC approach

A summary and EAG critique of the statistical approaches used to conduct the ITCs are provided in Table 14.

Table 14 EAG summary and critique of the company statistical approaches to adjusted ITCs

Item	EAG assessment	Summary of company approach	EAG comments
Were ITCs informed by relevant comparators?	Yes	The company conducted population-adjusted ITCs to compare the relative efficacy of crizotinib versus entrectinib (adjusted for potential confounding effects due to differences in baseline prognostic factors and treatment effect modifiers) using IPD from the pooled PROFILE 1001[20] and OxOnc[21] studies and aggregate-level data from pooled ALKA-372-001, STARTRK-1[53] and STARTRK-2[54] studies (reported by Drilon 2022[55]). Entrectinib was the only comparator listed in the final scope[19] issued by NICE and included in the company ITCs; statistical information relating to the pooled entrectinib studies is provided in the CS (CS, Table 9).	The EAG agrees with the inclusion of studies evaluating treatments which are relevant to the decision problem. The EAG agrees that, in the absence of head-to-head trial data, ITC methods are required to provide estimates of relative treatment effects between crizotinib and entrectinib. Additionally, the EAG notes that entrectinib is the only treatment currently recommended by NICE as part of routine commissioning for ROS1-positive advanced NSCLC.
Were adjusted ITCs conducted for all relevant outcomes?	Yes	The company carried out PFS, OS, DoR and ORR ITCs (CS; Section 3.12.1 to Section 3.12.4 and Appendix D.2). The company stated that the analysis of safety data was limited to descriptive assessment (CS, Section B.3.13).	The company did not conduct ITC analyses for safety/tolerability outcomes or PROs. The EAG considers that it is not possible to conduct meaningful ITC analyses of these outcomes due to low event rates and potential differences in assessment methods across the pooled PROFILE 1001[20] and OxOnc[21] trials, and pooled ALKA-372-001, STARTRK-1[53] and STARTRK-2[54] studies.
Adjustment for covariates	Partly	The company performed population-adjusted ITCs for four efficacy outcomes using IPD pooled across PROFILE 1001[20] and OxOnc[21] studies (denoted the index studies) through implementation of STC and MAIC approaches to overcome observed imbalances in study populations through outcome regression analyses (STC) or reweighting using a method-of-moments approach (MAIC). Baseline characteristics included in the base case STC were age, smoking status and ECOG PS. Three additional factors (sex, ethnicity and histological classification) were included in a sensitivity analysis. Lognormal, Gompertz and generalised gamma distributions were selected as the outcome regression models for PFS, OS and DoR, respectively, fitted to the pooled PROFILE 1001[20] and OxOnc[21] trial data, and outcomes were simulated for crizotinib within the entrectinib study population. In the MAIC, baseline characteristics prior to and after weighting crizotinib data were presented in the CS, Appendix D.2.3.5 (Table 27, p52), which included six characteristics (age, smoking status, ECOG PS, sex, ethnicity and histological classification). The company also performed a MAIC scenario excluding ethnicity.	Clinical advice to the EAG is that potentially important prognostic factors and treatment effect modifiers were included in the adjusted ITCs. However, advice also suggested that the presence of CNS metastases at baseline was an important factor; the company was unable to adjust for CNS metastases as relevant data were not available from the PROFILE 1001 trial. Additionally, there are observed differences regarding the number of prior regimens received across the studies; this has not been accounted for in the company's ITCs. The EAG agrees that after adjusting/weighting, baseline characteristics for patients in the pooled PROFILE 1001[20] and OxOnc[21] trials, and pooled ALKA-372-001, STARTRK-1[53] and STARTRK-2[54] studies were suitably balanced for some covariates; however, the EAG has concerns regarding the possibility of residual confounding due to observed and unobserved differences in study populations (for example, brain metastases at baseline and prior treatments).

Item	EAG assessment	Summary of company approach	EAG comments
Were adjusted ITC methods appropriate?	Partly	The methods used in the company adjusted ITCs are described in the CS (Section B.3.12 and Appendix D.2.2) and the company response to clarification question A9.	The EAG considers that the STCs and MAIC have been correctly implemented; however, the EAG has concerns about the robustness of the analyses. For example, the EAG has concerns that the selection of a different parametric model for PFS, OS or DoR could alter the ITC results; the impact of selecting different parametric distributions is not known. The EAG also has concerns regarding the accuracy of the digitisation process used to reconstruct IPD from the entrectinib studies for time-to-event outcomes including PFS, OS and DoR. In particular, the tails of reconstructed K-M curves presented in the company's MAICs (CS, Appendix D.2.3, Figure 19, Figure 23, Figure 26 and Figure 29) do not reflect the tails of the corresponding K-M curves published by Drilon 2022.[55] However, as part of the company's response to clarification question A7, the company presented new reconstructed K-M curves and these more accurately represent the corresponding published K-M curves. It is not clear which reconstructed data have been included in the company ITCs. If recreated data are inaccurate, this could bias the estimate of the treatment effect.
Was the PH assumption appropriately assessed within the adjusted ITCs of PFS and OS?	Yes	The company assessed the PH assumption for PFS and OS in the pooled PROFILE 1001[20] and OxOnc[21] trials and pooled ALKA-372-001, STARTRK-1[53] and STARTRK-2[54] studies using log-log and Schoenfeld residual plots (CS, Appendix D.2.3.5). The company found no statistically significant evidence of violation of the PH assumption but concluded that the PH assumption did not strictly hold and therefore the use of standard Cox models were relevant (CS, Appendix D.2.3.5).	The EAG agrees with the company that there was no statistically significant evidence of violation of the PH assumption. It is therefore not clear why the company generated time-varying STCs rather than constant STCs.
Was the presentation of adjusted ITC results appropriate?	Yes	The company presented an average time-varying HR in the main body of the CS; time-varying HRs (and 95% CIs), over a 7-year time frame (12-month intervals) were presented in Appendix D. The company also presented K-M curves and constant HRs (with 95% CIs) for PFS and OS for crizotinib versus entrectinib after MAIC weighting (CS, Section 3.12.6).	The presentation of company adjusted ITC results for all outcomes is appropriate. The company provided unadjusted ITC results in response to clarification question A2. The STC methods applied by the company result in the width of the 95% CIs around the time-varying HRs remaining approximately the same at all time points. Therefore, the 95% CIs estimated from the STC do not reflect the number of patients providing data at each time point (which diminishes over time); rather, they reflect the amount of data available overall. The EAG does not consider that it is appropriate to infer lack of statistical significance (or claims of similarity) from the 95% CIs from the STC. Further, the EAG notes that the company's ITCs are limited to

Item	EAG assessment	Summary of company approach	EAG comments
			unanchored comparisons only (in the absence of a common comparator arm); this approach relies on strong assumptions that the company has not investigated.

CI=confidence interval; CNS=central nervous system; CS=company submission; DoR=duration of response; EAG=External Assessment Group; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; IPD=individual patient data; ITC=indirect treatment comparison; K-M=Kaplan-Meier; MAIC=matching-adjusted indirect comparison; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazard; PRO=patient reported outcomes; ROS1=proto-oncogene tyrosine-protein kinase 1; STC=simulated treatment comparison
Source: CS, Section B.3.12, Appendix D; company response to clarification questions A2, A7 and A9

3.5.2 Studies included in the indirect comparisons

The company used crizotinib data pooled across PROFILE 1001[20] and OxOnc[21] trials (N=180) and entrectinib data from the Drilon[55] pooled analysis of the ALKA-372-001, STARTRK-1,[53] and STARTRK-2[54] trials (N=168). PROFILE 1001 trial median follow-up was 62.6 months (June 2018 DCO). Similarly, OxOnc[21] trial median follow-up was 56.1 months (July 2020 DCO). The most recent DCO for the entrectinib pooled analysis[55] was August 2020 (median follow-up time was 29.1 months); these data were used to inform the company's ITCs.

The company considered six trials for inclusion in the ITCs; individual patient data (IPD) were available from two crizotinib trials (the PROFILE 1001[20] trial and the OxOnc[21] trial) and aggregate-level entrectinib efficacy data were available from a pooled analysis[55] of three trials (ALKA-372-001, STARTRK-1,[53] and STARTRK-2[54] trials). The remaining trial, the B-FAST[60] trial, was described in an abstract that only reported ORR data; this trial was therefore not included in the company's ITCs.

Key characteristics of the patients enrolled in the PROFILE 1001[20] trial, the OxOnc[21] trial and the Drilon[55] trials are presented in Table 15. The characteristics of the patients enrolled in these trials differ:

- crizotinib trial data versus entrectinib trial data: ethnicity, ECOG PS and line of treatment (and in the OxOnc[21] trial there are fewer patients with CNS metastases than in the Drilon[55] pooled analysis)
- crizotinib trial data: ethnicity and ECOG PS
- entrectinib trial data: differences unclear due to lack of individual trial data

Table 15 Baseline characteristics of crizotinib and entrectinib trial patients

Characteristics	Crizotinib			Entrectinib
	PROFILE 1001[20] trial (N=53)	OxOnc[21] trial (N=127)	Pooled PROFILE 1001[20] & OxOnc[21] (N=180)	Drilon[55] pooled analysis (N=168)
Age, median (range), years	55 (25 to 81)	51.5 (22.8 to 79.7)	52.1 (22.8 to 81)	54.0 (20 to 86)
Male, n (%)	23 (43.4)	54 (42.5)	77 (42.8)	58 (34.5)
Ethnicity, n (%)				
Asian	21 (39.6)	127 (100)	148 (82.2)	78 (46.4)
Non-Asian	32 (60.4)	0	32 (17.8)	80 (47.6)
Other	0	0	0	2 (1.2)
NR	0	0	0	8 (4.8)
ECOG PS, n (%)				
0	23 (43.3)	34 (26.8)	57 (31.7)	66 (39.3)
1	29 (54.7)	93 (73.2)	122 (67.8)	86 (51.2)
2	1 (1.9)	0	1 (0.6)	16 (9.5)
Smoking status, n (%)				
No	40 (75.5)	91 (71.7)	131 (72.8)	108 (64.3)
Yes	13 (24.5)	36 (28.3)	49 (27.2)	60 (35.7)
Histological classification, n (%)				
Adenocarcinoma	51 (96.2)	124 (97.6)	175 (97.2)	163 (97.0)
Squamous cell carcinoma	1 (1.9)	1 (0.8)	2 (1.1)	1 (0.6)
NSCLC – NOS	1 (1.9)	2 (1.6)	3 (1.7)	4 (2.4)
Previous lines of treatment, n (%)[s]				
0	7 (13.2)	24 (18.9)	31 (17.2)	63 (37.5)
1	22 (41.5)	53 (41.7)	73 (40.6)	65 (38.7)
2	12 (22.6)	31 (24.4)	44 (24.4)	NR
3	NR	19 (15.0)	22 (12.2)	NR
≥2	24 (45.3)	NR	NR	40 (23.8)
≥3	12 (22.6)	19 (15.0)	31 (17.2)	
≥4	0 (0)	0 (0.0)	10 (5.6)	NR
Baseline CNS metastases, n (%)				
Measurable	NR	NR	NR	12 (7.1)
Present	NR	[redacted][b]	-	58 (34.5)
Not measurable	NR	NR	NR	46 (27.4)
Disease stage, n (%)				
Stage III	3 (5.7)	6 (4.7)	9 (5.0)	NR
Stage IV	50 (94.3)	121 (95.3)	171 (95.0)	NR

[a] PROFILE 1001 trial data for number of previous lines of treatment were extracted from CS, Table 8 and company response to clarification question A5
[b] The company reported (clarification question A5) that [redacted] ([redacted]) OxOnc[21] trial patients had brain metastases at baseline
CNS=central nervous system; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; NR=not reported; NSCLC=non-small cell lung cancer; NOS=not otherwise specified
Source: CS, Appendix D2.1, Table 13; company response to clarification question A13; Drilon 2022[55]

PROFILE 1001[20] and OxOnc[21] trial population characteristics that were most notably different from the Drilon[55] pooled analysis population characteristics were:

- the pooled PROFILE 1001[20] and OxOnc[21] trials included a higher proportion of Asian patients compared to the Drilon[55] pooled analysis
- the pooled PROFILE 1001[20] and OxOnc[21] trials included a higher proportion of patients with ECOG PS 1 and a lower proportion of patients with ECOG PS 2 compared to the Drilon[55] pooled analysis
- the pooled PROFILE 1001[20] and OxOnc[21] trials included a much lower proportion of first-line patients compared to the Drilon[55] pooled analysis
- the OxOnc[21] trial included a much lower proportion of patients with CNS metastases at baseline compared to the Drilon[55] pooled analysis.

The extent to which the differences between the pooled PROFILE 1001[20] and OxOnc[21] trials and the Drilon[55] pooled analysis might affect comparative results is unknown.

3.5.3 Indirect treatment comparison methodology and EAG critique

The company presented results from a series of ITCs conducted for three time-to-event (TTE) outcomes (OS, PFS, DoR) and one dichotomous outcome (ORR). The EAG agrees with the company that, due to the low number of events for AEs leading to treatment discontinuation, it was appropriate to limit the analysis of safety outcomes to a descriptive assessment.

As the PROFILE 1001[20] and OxOnc[21] trials are single-arm studies, and entrectinib data are based on a pooled analysis[55] of three single-arm studies (ALKA-372-001, STARTRK-1,[53] and STARTRK-2[54]), the company was unable to perform a network meta-analysis or anchored ITCs; these approaches rely on trials sharing a common comparator arm.

The company performed unanchored ITCs (STCs and MAICs). In response to clarification question A11, the company stated that an STC approach was preferred due to "…methodological and comparison-specific reasons". The company's base case STC only included three covariates (age, smoking status and ECOG PS). The company acknowledged the limitations of this approach and stated that there was "…potential bias of not adjusting for all prognostic factors and treatment effect modifiers" (company response to clarification question A11), particularly as the company identified "…poor overlap of population in terms of ethnicity" (CS, p63) when assessing the comparability of study populations. Specifically, a large proportion of patients in the two pooled crizotinib trials[20,21] were Asian (82.2%) compared to the entrectinib studies[55] (46.4%).

Unanchored ITCs (STCs and MAICs) were carried out using IPD from the pooled crizotinib trials[20,21] and aggregate-level data from the pooled entrectinib trials.[55]

The prognostic factors and treatment effect modifiers that the company adjusted for in the base case STCs were age, smoking status and ECOG PS. Additional prognostic factors and effect modifiers (ethnicity, sex and histological classification) were assessed in the 'full model' STC (sensitivity analyses) and in the MAICs (CS, Appendix D.2.3, p37). Clinical advice to the EAG is that the prognostic factors and treatment effect modifiers included in the ITCs were appropriate. The presence of baseline CNS metastases was also considered an important factor; however, the company was unable to adjust for CNS metastases as relevant data were not available from the PROFILE 1001 trial (CS, Appendix D.2.1, Table 13). In response to clarification question A10, the company stated that three variables (disease stage, baseline CNS metastases and number of prior regimens) could not be included in the ITCs due to missing data (i.e., "…covariates were reported in only one treatment arm"). The EAG notes that the number of prior regimens is reported for the crizotinib[20,21] and entrectinib[55] studies (defined as 0 versus 1 versus ≥2 prior therapies; CS, Appendix D.2.1, Table 13) and therefore this variable could have been included in the company's unanchored ITCs.

STCs

The company's STCs included an assessment of the relationship between baseline characteristics and outcomes using regression modelling. Specifically, for TTE outcomes, seven parametric curves (exponential, Weibull, lognormal, loglogistic, Gompertz, gamma and generalised gamma distributions) were fitted to the pooled PROFILE 1001[20] and OxOnc[21] trial data. The company stated that curve selection was based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) as well as on visual inspection of fit to the crizotinib Kaplan-Meier (K-M) curve. The company then applied backward elimination methods to the selected parametric curve to identify which factors to retain in the model. A crizotinib curve was estimated using the average population characteristics from the pooled entrectinib data to obtain an estimate of crizotinib within a population comparable to the pooled entrectinib trials.[55]

Entrectinib K-M curves[55] were digitised to reconstruct IPD. In response to clarification question A7, the company confirmed that digitisation was undertaken using WebPlotDigitizer and that IPD were reconstructed using the Guyot[67] algorithm. The same parametric curves selected to model pooled PROFILE 1001[20] and OxOnc[21] trial data were also used to model reconstructed entrectinib data. The EAG has concerns regarding the accuracy of the digitisation process used to reconstruct entrectinib data; specifically, the tails of the PFS, OS and DoR K-M curves have not been recreated (CS, Appendix D.2.3, Figure 19, Figure 23, Figure 26 and Figure 29). In response to clarification question A7, the company presented new reconstructed K-M curves that more accurately represent the corresponding published K-M curves;[55] however,

the tail of the company's new recreated OS K-M curve shows a lower proportion of patients surviving at 48 months compared to the published OS K-M curve.[55] As it is not clear which data have been included in the ITCs (STCs and MAICs), the EAG has concerns that erroneous or missing information could have biased the estimate of the treatment effect.

In response to clarification question A9, the company provided additional details regarding the approach used to estimate time-varying hazard ratios (HRs). After parametric survival modelling, hazard rates were computed per arm using the hazard function for the selected distribution per outcome of interest. The company used the lognormal curve to model PFS, the Gompertz curve to model OS and the generalised gamma curve to model DoR. The EAG agrees with the company that "…one of the main limitations of the STC is the potential bias introduced when choosing the survival parametric distribution" (CS, B.3.12.6, page 68); the impact of selecting a different parametric model to inform the ITC is not known. Further, the EAG considers that as the proportional hazard (PH) assumption was not violated, it would have been appropriate to explore STCs assuming constant hazards.

In response to clarification question A9, the company stated that "…the adjusted hazard rate of crizotinib was then divided by the hazard rate from entrectinib to obtain the time-varying HRs of crizotinib versus entrectinib" and the average HR was estimated as "…the mean time-varying HRs for a specific timeframe (i.e., 0 to 7 years)". The EAG considers that averaging time varying HRs is not appropriate as average ratios can obscure important temporal patterns and trends.

The company STC methods result in 95% CIs around the time-varying HRs that remain approximately the same width at all time points. These 95% CIs, therefore, do not reflect the number of patients providing data at each time point (which diminishes over time); rather, they reflect the amount of data available overall. Any claims that crizotinib and entrectinib are similar, that are based on non-statistically significant STC results, are not appropriate.

MAICs

The company also performed PFS and OS MAICs. Pooled PROFILE 1001[20] and OxOnc[21] trial IPD were re-weighted using a method-of-moments approach so that the average patient characteristics of pooled crizotinib data matched the average pooled entrectinib population characteristics. Cox regression modelling was then performed using reconstructed data to estimate HRs (crizotinib versus entrectinib).

A summary of baseline patient characteristics of the pooled crizotinib trials[20,21] (prior to- and after matching) and the pooled entrectinib trials[55] is presented in Table 16. After weighting, all

baseline characteristics included in the matching process were balanced between the two populations; the EAG highlights that it was not possible to adjust for CNS metastases at baseline. After weighting, the MAIC base case (based on adjustment for six factors) effective sample size (ESS) was 83.3 (46.3% of the original crizotinib sample size) and the MAIC excluding race ESS was 158.2 (87.9% of the original crizotinib sample size).

Table 16 Pooled crizotinib trials (prior to, and after, matching) and the pooled entrectinib trial baseline patient characteristics

Characteristics		Pooled PROFILE 1001 & OxOnc; crizotinib			Pooled ALKA-372-001, STARTRK-1 & STARTRK-2; entrectinib
		Before matching	After matching		
			MAIC base case	MAIC excluding race	
		N=180	ESS=83.3	ESS=158.2	N=168
Age, %	<54 years	52.2	50.0	50.0	50.0
	≥54 years	47.8	50.0	50.0	50.0
ECOG PS, %	0	31.7	39.3	39.3	39.3
	1	68.3	60.7	60.7	60.7
Race, %	Non-Asian	17.8	53.6	–	53.6
	Asian	82.2	46.4	–	46.4
Sex, %	Female	57.2	65.5	65.5	64.3
	Male	42.8	34.5	34.5	34.5
Smoking status, %	Previous smoker	27.2	35.7	35.7	35.7
	Never smoker	72.8	64.3	64.3	64.3
Histological classification, %	Adenocarcinoma	97.2	97.0	97.0	97.0
	Squamous cell	1.10	0.60	0.60	0.60
	Other histology	1.70	2.40	2.40	2.40

CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; MAIC=matching-adjusted indirect comparison
Source: CS, Appendix D.2.3.5, Table 27

The company rescaled the weights estimated in the matching process. Rescaled weights >1 means that an individual has more influence on results in the weighted population than in the original, unweighted population. The company inspected the distribution of rescaled weights (CS, Appendix D.2.3.5, Figure 18); two patients were associated with a rescaled weight above five.

The company assessed the validity the PH assumption for PFS and OS. The Cox PH model is considered appropriate where there is no violation of the PH assumption. The company assessed log-cumulative hazard and Schoenfeld residual plots (CS, Appendix D.2.3, Figure 20, Figure 21, Figure 24, Figure 25, Figure 27, Figure 28, Figure 30 and Figure 31) and concluded that whilst the PH assumption is not strictly holding for PFS and OS (due to K-M curves crossing), the results from standard Cox models were useful (CS, Section D.2.3, p54).

The EAG agrees with the company that there was no statistically significant evidence of violation of the PH assumption.

3.5.4 Indirect comparison results

STC: PFS

The lognormal distribution was selected to model PFS. Crizotinib and entrectinib PFS K-M curves are presented in Figure 1, along with the entrectinib and adjusted crizotinib lognormal curves.

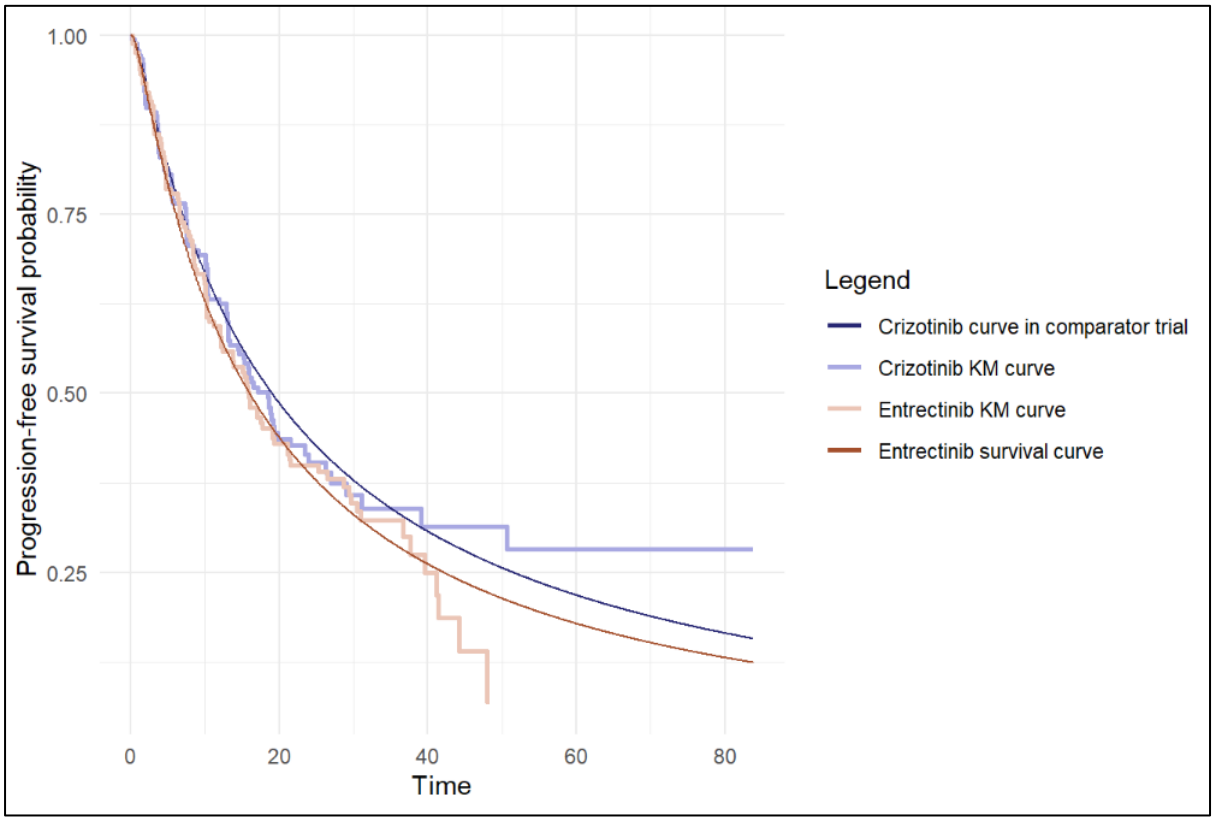

Figure 1 PFS K-M curves: entrectinib and adjusted crizotinib lognormal curves

K-M=Kaplan-Meier; PFS=progression-free survival
Source: CS, Figure 6

The company base case (adjustment for three covariates) time-varying PFS HRs (crizotinib versus entrectinib) are presented in Table 17. These PFS results were numerically favourable but non-significant for crizotinib, with 95% CIs including a HR estimate of 1.0. The company also provided (CS, Appendix D.2.3.1, p36) the average HR ([redacted] over a 7-year timeframe). When adjusting for six covariates (full STC model), the average HR was [redacted] (CS, Appendix D.2.3.1, p37). The corresponding crizotinib and entrectinib K-M curves, and the entrectinib and adjusted crizotinib lognormal curves, were presented in the CS (CS, Appendix D.2.3, Figure 5). Whilst the average time-varying PFS HR is similar to the PFS HR for each time period, the EAG considers that it is not appropriate to average time-varying HRs.

To explore robustness, the company carried out analyses that included adjustments for six covariates; the average time-varying PFS HR result is available in the CS (Appendix D).

STC: OS

The Gompertz distribution was used to model OS. Crizotinib and entrectinib OS K-M curves are presented in Figure 2, along with the entrectinib and adjusted crizotinib Gompertz curves.

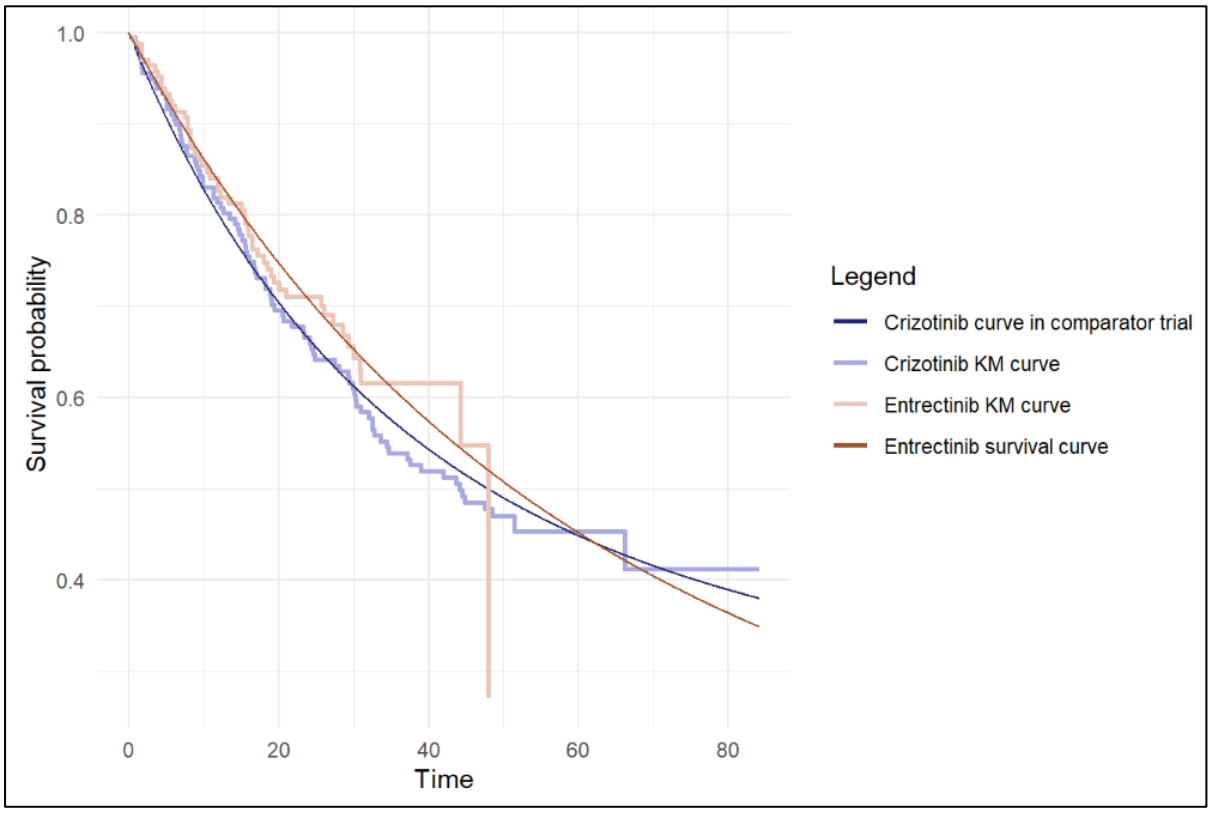

Figure 2 OS K-M curves and entrectinib and adjusted crizotinib Gompertz curves

K-M=Kaplan-Meier; OS=overall survival
Source: CS, Figure 7

The company base case (adjustment for three covariates) time-varying OS HRs (crizotinib versus entrectinib) are presented in Table 17. The average time-varying HR was estimated as [redacted] over a 7-year timeframe (CS, Appendix D.2.3.2, p42). In the full STC model, the average HR was [redacted] (CS, Appendix D.2.3.2, p43). The corresponding crizotinib and entrectinib K-M curves and the entrectinib and adjusted crizotinib Gompertz curves are also presented by the company (CS, Appendix D.2.3.2, Figure 10).

The EAG considers that it is not appropriate to average time-varying HRs. The OS HR starts high and decreases over time (Table 17); the average HR over the 7-year time periods misrepresents the risk at any specific point in time and provides misleading information about the relative effectiveness of crizotinib versus entrectinib; an average time-varying HR can mask the true treatment effect and should not be used to inform decision making.

The EAG highlights that the OS K-M data provided by the company (Figure 2) show that up to approximately 30 months, OS is better for patients treated with entrectinib than for patients treated with crizotinib; after approximately 30 months, only limited entrectinib data are available. Over the first 24 months, company numerical point estimates (Table 17) also favour entrectinib over crizotinib.

To explore robustness, the company carried out analyses that included adjustments for six covariates; the average time-varying OS HR result is available in the CS (Appendix D).

Table 17 Company base case PFS and OS STC results (crizotinib versus entrectinib)

Outcome	Time-varying HRs (95% CI)[a]						
	12 months	24 months	36 months	48 months	60 months	72 months	84 months
PFS	[redacted]						
OS	[redacted]						

[a] HR<1 indicates an advantage to crizotinib. The EAG does not consider that it is appropriate to infer statistical significance (or lack of) from the 95% CIs estimated in the STC
CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; STC=simulated treatment comparison
Source: CS, Appendix D.2.3, Table 17 and Table 21

STC results using data from PROFILE 1001 and OxOnc trials individually

In response to clarification question A12, the company provided STC results from individual PROFILE 1001[20] and OxOnc[21] trial data versus pooled entrectinib trial data. These results raised concerns about the robustness of company STC results generated using pooled PROFILE 1001[20] and OxOnc[21] trial data. For example, the time-varying PFS HRs for the comparison of crizotinib versus entrectinib are always lower when using pooled PROFILE 1001[20] and OxOnc[21] trial data than when using individual PROFILE 1001[20] and OxOnc[21] trial data. The time-varying OS HRs for the comparison of crizotinib versus entrectinib after 48 months are always lower when using pooled PROFILE 1001[20] and OxOnc[21] trial data than when using individual PROFILE 1001[20] and OxOnc[21] trial data.

STC: DoR and ORR

The company base case (adjustment of three covariates) time-varying OS HRs (crizotinib versus entrectinib) are presented in Table 18. DoR and ORR results favour crizotinib but are not statistically significant. All associated 95% CIs are wide and include a HR of 1 (Table 18).

To explore robustness, the company carried out analyses that included adjustments for six covariates; all results are available in the CS (Appendix D).

Table 18 Company base case DoR and ORR STC results for crizotinib versus entrectinib

Outcome	Time-varying ratios (95% CI)[a]						
	12 months	24 months	36 months	48 months	60 months	72 months	84 months
DOR (HR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR (OR)	Base case: [redacted]						

[a] HR<1 indicates an advantage to crizotinib. The EAG does not consider that it is appropriate to infer statistical significance (or lack of) from the 95% CIs estimated in the STC
CI=confidence interval; DoR=duration of response; HR=hazard ratio; OR=odds ratio; ORR=objective response rate; STC=simulated treatment comparison
Source: CS, Appendix D.2.3.3 and Appendix D.2.3.4, Table 25

MAICs

Company MAIC results are presented in Table 19. The company did not present unadjusted MAIC results in the CS; however, these results were submitted in response to clarification question A2. The EAG considers that it is useful to inspect the unadjusted results as these give an indication of the impact of the population adjustments on results. PFS and OS K-M curves prior to, and after, weighting are presented in the CS (Appendix D.2.3, Figure 19, Figure 23, Figure 26 and Figure 29).

All PFS results numerically favour crizotinib and all OS results numerically favour entrectinib; none of the results were statistically significant and all confidence intervals were wide.

Table 19 Company PFS and OS MAIC results (crizotinib versus entrectinib)

Crizotinib versus entrectinib	PFS		OS	
	HR (95% CI)		HR (95% CI)	
	Unadjusted	After weighting	Unadjusted	After weighting
MAIC base case	[redacted]	[redacted]	[redacted]	[redacted]
MAIC excluding race		[redacted]		[redacted]

CI=confidence interval; CS=company submission; HR=hazard ratio; MAIC=matching-adjusted indirect comparison; OS=overall survival; PFS=progression-free survival
Source: CS, p69 and company response to clarification question A2

The base case MAIC and the MAIC excluding race results were similar despite a reduction in the ESS. Unadjusted estimates were similar to adjusted estimates, which suggests that residual confounding due to lack of adjustment for all prognostic factors and treatment effect modifiers may be present.

3.5.5 EAG additional comments on company indirect comparisons

The EAG considers that the methods used by the company to conduct STCs and MAICs were generally appropriate.

Differences in baseline patient characteristics, trial design, outcome definitions and outcome follow-up periods may have introduced heterogeneity into the ITCs; the impact of any heterogeneity is unknown.

The company base case ITC approach was to generate results using STCs; this approach was selected to avoid a highly reduced ESS often associated with MAICs. The EAG highlights that the company MAIC ESSs remain reasonably large relative to the original sample size. Further, the company base case STCs do not adjust for ethnicity, despite this covariate providing the company's justification for selecting the STC approach; the company recognised that ethnicity was important due to differences in ethnicity between the crizotinib and entrectinib populations. Despite the company's responses to clarification questions A10 and A11, the EAG considers that the base case ITCs should have included all covariates that are considered prognostic of outcomes and/or treatment effect modifiers; however, the EAG acknowledges that company full model STC results, which adjusted for six covariates, generated results that were similar to base case results. The EAG considers that company MAIC results are more informative than company STC results as statistical significance should not be inferred from the STC CIs. In addition, after weighting, all matching-adjusted baseline characteristics (n=6) were balanced between the two populations. The EAG highlights, however, that not all covariates were adjusted for (i.e., number of prior lines of treatment and CNS metastases at baseline) in any of the ITCs.

In summary, when considering the company's ITC results, it is important to note the following issues:

- adjustments were not made to account for differences in all identified prognostic factors and treatment effect modifiers (CS, Appendix D.2.1, p28)
- the CS did not include any discussion about the amount of residual confounding likely to be present in the ITCs; only three (out of a possible six) covariates were adjusted for in the company base case STCs (CS, Section B.3.12.1, p63)
- it is not known to what extent the lack of adjustment for additional prognostic factors and/or treatment effect modifiers affect ITC results
- the ITC approach (STCs and MAICs) is limited to unanchored comparisons and relies on strong assumptions which are unlikely to be fulfilled
- the crizotinib OxOnc[21] trial only enrolled Asian patients; the generalisability of the ITC results generated using these data to NHS patients is unclear
- the width of the 95% CIs around estimated treatment effects, particularly for OS, reflect a large amount of uncertainty

- it is not appropriate to average time-varying HRs
- there are concerns regarding pooling data across the studies used in the ITCs, particularly due to the heterogeneous nature of the study populations.

Due to the limitations of the company's ITCs, the EAG considers that the reported comparative efficacy estimates may not represent the true underlying treatment effect of crizotinib versus entrectinib for the treatment of confirmed ROS1-positive advanced NSCLC. The PFS MAIC HR point estimate favours crizotinib and the OS MAIC HR point estimate favours entrectinib, and both CIs include 1. There is ongoing debate around whether CIs that include 1 should be used to support claims of similar health benefits.

3.6 OxOnc and EUCROSS trial patient reported outcomes

HRQoL data were only collected in the OxOnc[21] and EUCROSS[58] trials (CS, Section 3.7.5). In the OxOnc[21] trial, HRQoL data (n=123/127) were collected at baseline, at Cycle 1 and every cycle up to Cycle 8, and then at every other cycle until end of treatment.[66] In the EUCROSS[58] trial, HRQoL data (n=31/34) were collected at baseline and then every two cycles up to Cycle 24. The OxOnc[21] and EUCROSS[58] trials collected HRQoL data using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) questionnaire and the EORTC QLQ-lung cancer module (EORTC QLQ-LC13).

The company reported the proportions of OxOnc[21] trial patients who experienced a clinically meaningful improvement (i.e., ≥10 point increase) or a clinically meaningful worsening (i.e., ≥10 point decrease) of EORTC QLQ C-30 and EORTC QLQ LC-13 scores from baseline. At Cycle 20 most patients experienced either a clinically meaningful improvement in global health status (GHS) score ([redacted]) or a stable GHS score (<10 point change; [redacted]).[65] Similarly, at most timepoints, most patients (>50%) experienced either a clinically meaningful improvement or a stable score for all five EORTC QLQ C-30 functional scales (physical, role, cognitive, emotional, and social).[21] During the period between Cycle 2 and Cycle 60, the highest proportions of patients reported clinically meaningful improvements in five EORTC QLQ-C30 symptom scores (appetite loss, fatigue, dyspnoea, insomnia and pain) and four EORTC QLQ-LC13 symptom scores (coughing, chest pain, dyspnoea and arm or shoulder pain).[21]

The EUCROSS[58] trial only reported mean EORTC QLQ C-30 and EORTC QLQ LC-13 scores and did not report the numbers of patients who experienced clinically meaningful improvement or clinically meaningful worsening. Patient EORTC QLQ C-30 GHS scores, and all other mean QLQ-C30 functioning scales (with the exception of cognitive functioning) improved over time but changes from baseline were not statistically significant. In contrast to the OxOnc[21] trial,

mean EUCROSS[58] trial EORTC QLQ-C13 symptom scores for coughing, dyspnoea and chest pain worsened over time.

3.7 Safety and tolerability results from the PROFILE 1001, OxOnc and EUCROSS trials

Key PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trial safety results are presented in Section 3.7.1 and Section 3.7.2.

In the PROFILE 1001 trial (30 June 2018 DCO), 12/53 (22.6%) patients remained on crizotinib treatment, and in the EUCROSS[58] trial (24 January 2018 DCO), 8/34 (23.5%) patients remained on crizotinib treatment; the proportion of OxOnc trial (30 July 2016 DCO) patients who remained on crizotinib treatment was not reported. Median duration of crizotinib treatment was 22.4 months in the PROFILE 1001[20] trial, 23.4 months in the OxOnc[21] trial and 22.8 months in the EUCROSS[22] trial. The PROFILE 1001[20] trial dose reduction rate was not reported; the dose reduction rate was notably lower in the OxOnc[21] trial (n=22/127, 17.3%) than in the EUCROSS[58] trial (n=16/34, 47.1%).

3.7.1 Treatment-related adverse events

All PROFILE 1001[20] trial patients experienced ≥1 any Grade treatment-related adverse event (TRAE) and nearly all OxOnc[21] and EUCROSS[58] trial patients (97.6% and 97.1%, respectively) experienced ≥1 any Grade TRAE. Most TRAEs were Grade 1 or Grade 2 (CS, p70).

In the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trials, three of the most commonly reported TRAEs (any Grade) were vision disorders (48.0% to 86.8%), nausea (41.7% to 51%) and diarrhoea (41.7% to 56%). Other commonly reported TRAEs (any Grade) were oedema (47.2% to 50.0%), elevated transaminases (66.9%) and bradycardia (47.1%).

In the PROFILE 1001,[20] OxOnc[21] and EUCROSS[58] trials, 26.5% to 35.8% of patients experienced ≥1 Grade 3 TRAE. Neutropenia/leukopenia was the most common Grade 3 TRAE in the OxOnc[21] (n=12/127, 9.4%) and EUCROSS[58] (n=3/34, 8.8%) trials and hypophosphatemia was the most commonly reported Grade 3 TRAE in the PROFILE 1001[20] trial (n=8/53, 15.1%). Hypophosphatemia is the only AE that is included in the company cost comparison analysis.

No patients in the PROFILE 1001[20] trial, only 3/127 (2.4%) patients in the OxOnc[21] trial and 2/34 (5.9%) patients in the EUCROSS[58] trial discontinued treatment with crizotinib due to AEs.

3.7.2 Death

No patients in the PROFILE 1001[20] trial and only one patient in each of the OxOnc[21] and EUCROSS[58] trials experienced a Grade 5 TRAE (i.e., death). Cause of death in the OxOnc[21] trial was respiratory failure (the investigator reported the relationship as unknown and therefore the cause of death was considered treatment-related) and the cause of death in the EUCROSS[58] trial was pulmonary embolism.

3.7.3 Comparison of crizotinib and entrectinib TRAEs

Comparative crizotinib and entrectinib any grade TRAEs occurring ≥10% of all safety evaluable patients) are presented in Table 20. These data show that, most notably for vision disorder, oedema, elevated transaminases and bradycardia, the incidence of each TRAE is not always consistent across the crizotinib trials. Data reported from the Drilon[55] pooled analysis show that the frequencies of TRAEs experienced by patients treated with entrectinib differ from the frequencies of TRAEs experienced by patients treated with crizotinib. Due to data availability it has not been possible to robustly compare Grade ≥3 TRAEs.

Table 20 Comparative crizotinib and entrectinib TRAEs (≥10% of safety evaluable patients)

TRAEs (any grade), n (%)	Crizotinib			Entrectinib
	PROFILE 1001[20] trial (N=53)	OxOnc[21] trial (N=127)	EUCROSS[58] trial (N=34)	Drilon[55] pooled analysis (N=224)
Vision disorder	46 (87)	61 (48.0)	22 (65)	Blurred vision: 12 (5.4)
Nausea	27 (51)	53 (41.7)	14 (41)	45 (20.1)
Oedema	25 (47)	34 (26.8)	17 (50)	Peripheral: 48 (21.4) Generalised: 5 (2.2)
Diarrhoea	24 (45)	53 (41.7)	19 (56)	68 (30.4)
Vomiting	20 (38)	43 (33.9)	11 (32)	35 (15.6)
Elevated transaminases	19 (36)	85 (66.9)	AST: 9 (26) ALT: 12 (35)	AST: 27 (12.0) ALT: 26 (11.6)
Constipation	18 (34)	41 (32.3)	5 (15)	71 (31.7)
Increased weight	NR	NR	NR	77 (34.4)
Bradycardia	11 (21)	14 (11)	16 (47)	NR
Fatigue	11 (21)	15 (11.8)	Asthenia/ fatigue: 6 (18)	62 (27.7)
Blood creatine increased	NR	25 (19.7)	7 (21)	49 (21.8)
Dizziness	10 (19)	NR	5 (15)	83 (40.0)
Dysgeusia	10 (19)	17 (13.4)	4 (12)	91 (40.6)
Paraesthesia	NR	NR	NR	41 (18.3)
Myalgia	NR	NR	NR	37 (16.5)
Hypophosphatemia	9 (17)	NR	NR	3 (1.3)
Decreased appetite	8 (15)	22 (17.3)	NR	11 (4.9)
Leukopenia	Neutropenia: 8 (15)	Leukopenia: 33 (26.0) Neutropenia: 43 (33.9)	Leukopenia/ neutropenia: 11 (32)	Neutropenia: 10 (4.4)
Abdominal pain	NR	NR	5 (15)	NR
Anaemia	NR	NR	5 (15)	30 (13.4)
Rash	7 (13)	NR	NR	19 (8.4)
Blood AP increased	NR	13 (10.2)	4 (12)	NR
Arthralgia	NR	NR	NR	27 (12.1)
Dysphagia	NR	NR	NR	23 (10.3)

ALT=alanine transaminase; AP=alkaline phosphatase; AST=aspartate transaminase; NR=not reported; TRAE=treatment-related adverse event;
Source: CS, Table 19

3.7.4 EAG safety conclusions

Clinical advice to the EAG is that crizotinib is tolerable and that the AEs associated with crizotinib are manageable in NHS clinical practice. The frequencies of TRAEs experienced by patients treated with entrectinib differ from the frequencies of TRAEs experienced by patients treated with crizotinib.

3.8 Conclusions of the clinical effectiveness section

Only data from single-arm, non-randomised (mostly small sample size) studies are available to demonstrate the clinical effectiveness of crizotinib.

The EAG considers that, overall, company STC and MAIC methods are appropriate, however there are still concerns. On balance, the EAG considers that company MAIC results are more informative that company STC results. Numerically, MAIC PFS results favour crizotinib but OS results favour entrectinib.

The EAG considers that the key areas of uncertainty are as follows:

Crizotinib data

- Only 1% to 2% of patients with advanced NSCLC have ROS1-positive disease;[12] currently there is no randomised trial evidence for the comparison of crizotinib versus any comparator. The single-arm crizotinib trial evidence is heterogeneous and in the pooled PROFILE 1001[20] trial and OxOnc[21] trial dataset the majority of patients were Asian.
- It is likely that, if recommended by NICE, crizotinib will be used in the NHS in the first-line setting; however, none of the crizotinib trials[20-22] and only 4/16 real-world crizotinib studies[30,34-36] only included patients with previously untreated ROS1-positive advanced NSCLC.
- It is not clear why SACT dataset[25] median OS is shorter than median OS in the three crizotinib trials (PROFILE 1001,[20] OxOnc[21] and EUCROSS[22] trials); the difference between PROFILE 1001[20] trial and SACT dataset[25] OS results requires further consideration by the company.
- Clinical expert opinion supports the anticipated benefit of entrectinib (versus crizotinib) for patients with CNS metastasis; however, there are few data to corroborate this advantage, and/or to evidence how this benefit might translate into delaying overall disease progression, and ultimately improve survival (TA643 ERG report[51]).

STC results

- The EAG considers that as STC 95% CIs do not reflect the number of patients providing data at each time point (which diminishes over time); rather, they reflect the amount of data available overall, it is not appropriate to infer lack of statistical significance (or claims of similarity) from the STC 95% CIs.
- The company has presented STC average time-varying HRs. The EAG considers that it is not appropriate to average time-varying HRs and these results should not be used to inform decision-making.

STC and MAIC results

- The company did not adjust for either line of treatment or brain metastases in the STCs or MAICs; the EAG considers that it was possible to adjust for line of treatment.
- The EAG also highlights that the PFS MAIC HR point estimate favours crizotinib and the OS MAIC HR point estimate favours entrectinib and both CIs include 1; however, there is ongoing debate around whether CIs that include 1 should be used to support claims of similar health benefits.

4 EAG SUMMARY AND CRITIQUE OF COST EFFECTIVENESS EVIDENCE

4.1 Company cost comparison

The company has carried out a cost comparison to compare the cost effectiveness of crizotinib versus entrectinib for patients with ROS1-positive advanced NSCLC.

4.1.1 Summary of costs and assumptions

Key inputs and assumptions used in the company base case and scenario analyses are shown in Table 21 and Table 22, respectively. Costs were calculated over a lifetime horizon (20 years); in the model submitted by the company, the time horizon can be varied up to a maximum of 40 years.

The company has assumed that drug monitoring costs, drug administration costs, post-progression costs and time on treatment are the same for patients treated with crizotinib and patients treated with entrectinib; therefore, differences in costs only arise from differences in drug acquisition and AE costs. The company explained (CS, p79) that, for patients treated with crizotinib, the only Grade ≥3 AE that occurs in at least 5% of patients and requires medical resource, is hypophosphatemia.

Table 21 Company cost comparison base case analysis: key inputs

Input name	Base case value	Source
Crizotinib cost (per year, PAS price)	[redacted]	CS, Table 22
Entrectinib (per year, list price)	£62,823	BNF[68]
Hypophosphatemia (1 hospitalisation day)	£535.97	NHS Cost Collection[69]

BNF=British National Formulary; CS=company submission; NHS=National Health Service; PAS=Patient Access Scheme
Source: CS, Table 22 and Table 24

Table 22 Company cost comparison analysis: key assumptions

Assumption	Company rationale for assumption	Related scenario analyses
Time horizon=20 years.	This is long enough to capture all treatment-related costs.	Time horizon of 10 years and 30 years.
Only costs for Grade 3 and Grade 4 AEs experienced by ≥5% of patients are included in the model.	Established practice in health economic modelling.	Inclusion of Grade 3 and Grade 4 AEs experienced by ≥2% of patients.
Monitoring costs (based on TA529[62] resource used, updated using 2021/22 NHS Cost Collection costs)[69] are the same for patients treated with crizotinib and patients treated with entrectinib.	Clinical feedback to the company was that monitoring would be the same for patients treated with crizotinib and patients treated with entrectinib. The TA529[1] NICE Appraisal Committee accepted the monitoring costs used in the company model.	Alternative costs proposed by the TA643[51] ERG.
Treatment duration is the same for patients treated with crizotinib and patients treated with entrectinib. Treatment duration was estimated by using a Lognormal distribution fitted to PROFILE 1001[20] trial PFS data.	PFS is an appropriate proxy for TTD.	Alternative distributions fitted to PROFILE 1001[20] trial PFS data.
Post-progression treatments are the same for patients treated with crizotinib and patients treated with entrectinib.	Following NICE clinical guideline pathway.	None.

AE=adverse event; CS=company submission; ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: CS, Section B.4.2

4.1.2 Company cost comparison analysis results

Company base case results are shown in Table 23. Using the PAS price for crizotinib and the list price for entrectinib, the company estimated that, over 20 years, treatment with crizotinib would cost [redacted] less than treatment with entrectinib.

Table 23 Company base case results (total per person costs over a 20-year time horizon, PAS price for crizotinib and list price for entrectinib)

Treatment	Crizotinib	Entrectinib
Acquisition	[redacted]	£253,295
Administration	£899	£899
Monitoring	£12,263	£12,263
AE management	£81	£0
Total cost	[redacted]	**£266,457**
Incremental cost	-	[redacted]

AE=adverse event; CS=company submission; PAS=Patient Access Scheme
Source: CS, Table 28

The company carried out the following scenario analyses:

- alternative distributions used to extrapolate PFS data (CS, Table 30)
- TA529[62] ERG's preferred approach to estimating resource use associated with monitoring (CS, Table 31)
- time horizons of 10 years and 30 years (CS, Table 32)
- inclusion of AEs occurring in at least 2% of patients (CS, Table 33).

Using alternative distributions to extrapolate PFS (and therefore time on treatment) increased the amount that crizotinib was cost-saving when, compared to the base case, the alternative distribution increased PFS and decreased the amount crizotinib was cost-saving when, compared to the base case, the alternative distribution decreased PFS. Using the Gompertz distribution to extrapolate PFS resulted in the largest cost saving ([redacted]) and using the exponential distribution to extrapolate PFS resulted in the smallest cost-saving ([redacted]).

Using alternative resource use/monitoring costs made no difference to the extent that crizotinib was cost-saving.

A shorter time horizon resulted in reductions in the extent that crizotinib was cost-saving and a longer time horizon increased the extent that crizotinib was cost-saving. Using a 30-year time horizon resulted in the highest cost saving ([redacted]) and using a 10-year time horizon resulted in the smallest cost-saving ([redacted]).

Compared with the base case, the inclusion of AE management costs for AEs occurring in at least 2% of patients reduced the extent that crizotinib was cost-saving by just [redacted].

Cost comparison results from all scenarios presented by the company showed that, compared with entrectinib, treatment with crizotinib was cost-saving.

4.2 EAG critique of company cost comparison

It is stated in the final scope[19] issued by NICE that, 'If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out'. The EAG considers that the following two elements should be considered when assessing similarity:

- similarities and differences between crizotinib and entrectinib
- clinical effectiveness evidence (ITCs: crizotinib versus entrectinib)

4.2.1 Similarities and differences between crizotinib and entrectinib

In response to clarification question A1, the company provided information to compare crizotinib and entrectinib (Table 24). Key differences between the two drugs are:

- crizotinib primarily targets ALK, ROS1 and c-MET, whilst entrectinib targets ALK, ROS1 and TRK receptors
- crizotinib has a longer half-life (42 hours) compared to entrectinib (20 hours) and the two drugs differ in terms of frequencies of any grade TRAEs (see Table 20).

Table 24 Comparison of the similarities and differences between crizotinib and entrectinib

Item	Crizotinib	Entrectinib
Mechanism of action	Crizotinib is a potent inhibitor ALK, ROS1, and c-MET. By binding to the ATP-binding site of these kinases, crizotinib prevents their activation and downstream signalling, thereby inhibiting tumour growth and survival.	Entrectinib inhibits ALK, ROS1, and c-MET, and targets TRK receptors. Entrectinib blocks the activation of these kinases, leading to the disruption of signalling pathways involved in cancer cell proliferation and survival.
Pharmacology	Crizotinib and entrectinib are both type 1 non-cyclic compounds	
Pharmacokinetic properties	Crizotinib is extensively metabolized in the liver, primarily via the cytochrome P450 enzyme CYP3A4/5. It has a relatively long elimination half-life of approximately 42 hours. Crizotinib is mainly eliminated through faeces (63%) and to a lesser extent through urine (22%).	Entrectinib is also predominantly metabolized by pre CYP3A4 (its major active metabolite is M5) and this is highly bound to human plasma proteins independent of drug concentrations. The elimination half-lives of entrectinib and M5 were estimated to be 20 hours and 40 hours, respectively. Entrectinib is eliminated through both faeces (84%) and urine (11%).
Administration	Crizotinib is administered twice daily.	Entrectinib is administered once daily.
Metabolisation	Crizotinib and entrectinib are metabolised by similar liver enzymes, including CYP3A4	

ALK=anaplastic lymphoma kinase; ATP=adenosine triphosphate; c-MET=mesenchymal-epithelial transition factor; ROS1=proto-oncogene tyrosine-protein kinase 1; TRK=tropomyosin receptor kinase
Source: Company response to clarification question A1

4.2.2 Clinical effectiveness evidence (ITCs: crizotinib versus entrectinib)

The company has generated STC and MAIC results to compare the effectiveness of crizotinib versus entrectinib. None of the results statistically significantly favoured crizotinib over entrectinib. The company has assumed that as all the STC and MAIC results have wide CIs that include 1, this suggests that the efficacy of crizotinib and entrectinib is similar. However, rather than confirming similarity, the EAG considers that CIs describe the uncertainty inherent in the point estimate and indicate the range of values within which the reader can be reasonably sure that the true effect lies. The EAG, therefore, considers that the company ITC results have not conclusively demonstrated that the effectiveness of crizotinib is similar to the effectiveness of entrectinib; this means that it is not clear if a cost comparison approach is appropriate.

4.2.3 EAG critique of company cost comparison methods

The company has assumed, based on the presented efficacy and safety evidence, that outcomes for patients treated with crizotinib and patients treated with entrectinib are similar (CS, p19). Therefore, the only parameters that can affect differences in cost are AE costs, monitoring costs and time on treatment.

The frequencies of individual any grade TRAEs differ for patients treated with crizotinib and for patients treated with entrectinib. The company approach, which results in higher AE costs for patients treated with crizotinib than for patients treated with entrectinib may be conservative. However, AE costs per patient are very low and varying AE costs in the model has a minimal effect on total costs.

Clinical advice to the company, and to the EAG, is that monitoring costs for patients treated with crizotinib and monitoring costs for patients treated with entrectinib are the same.

If the NICE Appraisal Committee considers that all important outcomes (efficacy and safety) for patients treated with crizotinib and patients treated with entrectinib are similar, then the EAG is satisfied that time on treatment will also be the same. If outcomes are similar, the choice of how to model time on treatment (via PFS) only has an impact on total costs, not on the difference between crizotinib and entrectinib costs. Therefore, if the assumption that all important outcomes are similar holds, the only parameter that can affect cost comparison results is the cost to the NHS of purchasing crizotinib and entrectinib.

4.3 EAG cost comparison results

The EAG is satisfied that the company cost comparison analysis methods were appropriate and, therefore, has not generated alternative cost comparison results. Cost effectiveness results using the PAS prices for crizotinib and entrectinib are presented in a confidential appendix.

4.4 EAG conclusion

If the NICE Appraisal Committee considers that crizotinib and entrectinib are similar and that, for decision making purposes, any differences in patient outcomes can be ignored, then the EAG considers that company cost comparison results are robust.

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6 APPENDICES

6.1 Appendix 1 Quality assessment of the PROFILE 1001, OxOnc and EUCROSS trials

Table 25 Quality assessment for the PROFILE 1001, OxOnc and EUCROSS trials

	Company assessment			EAG assessment			EAG comment
Quality assessment item	**PROFILE 1001[20] trial**	**OxOnc[21] trial**	**EUCROSS[22] trial**	**PROFILE 1001[20] trial**	**OxOnc[21] trial**	**EUCROSS[22] trial**	
1. Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	
2. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Cannot tell	Cannot tell	Cannot tell	All three trials[20-22] had clear and pre-specified inclusion and exclusion criteria; however, recruitment methods were not reported
3. Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes	
4. Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes	
5a. Have the authors identified all important confounding factors?	Cannot tell	Cannot tell	Cannot tell	Yes	No	Yes	Subgroup analyses were conducted in all three trials;[20-22] only OxOnc[21] and EUCROSS[22] provided results for patients with/without CNS metastases
5b. Have they taken account of the confounding factors in the design and/or analysis?	Cannot tell	Cannot tell	Cannot tell	Yes	No	Yes	
6a. Was the follow up of subjects complete enough?	Yes	Yes	Yes	Yes	Yes	Yes	
6b. Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Yes	Yes	

	Company assessment			EAG assessment			EAG comment
Quality assessment item	**PROFILE 1001[20] trial**	**OxOnc[21] trial**	**EUCROSS[22] trial**	**PROFILE 1001[20] trial**	**OxOnc[21] trial**	**EUCROSS[22] trial**	
7. What are the results of this study?	Results supported the view that crizotinib treatment is effective and safe for patients with ROS1-positive NSCLC						Patients with ROS1-positive NSCLC treated with crizotinib tolerated treatment and, across the trials,[20-22] the ORR was 70% to 72%. However, the trials did not provide comparative evidence versus the relevant comparator (entrectinib)
8. How precise are the results?	Yes	Yes	Yes	Yes	Yes	Yes	Results were precise and 95% CIs were reported for key efficacy outcomes (ORR, median DoR, median PFS and median OS)
9. Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Median follow-up was sufficient, and the results were precise
10. Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	• Clinical advice to the EAG is that the baseline patient characteristics in the three crizotinib trials[20-22] are broadly representative of NHS patients with ROS1-positive NSCLC • Only a small proportion of trial patients were treated with crizotinib in the first-line setting • More patients were Asian in the PROFILE 1001[20] trial than in NHS clinical practice and all OxOnc[21] trial patients were Asian
11. Do the results of this study fit with other available evidence?	Yes	Yes	Yes	No	No	No	Real-world study ORR results were consistent with the trial results; however, real-world study median OS results varied substantially (21.9 months [SACT dataset[25]] to 60 months [Zheng 2020[36]]).
12. What are the implications of this study for practice?	The study findings serve as a new benchmark for OS in ROS1-rearranged advanced NSCLC and continue to show the clinically meaningful benefit and safety of crizotinib			Cannot tell	Cannot tell	Cannot tell	All the trial results appear to support the use of crizotinib for patients with ROS1-positive advanced NSCLC

CI=confidence interval; DoR=duration of response; EAG=External Assessment Group; NHS=National Health Service; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; ROS1=proto-oncogene tyrosine-protein kinase 1; SACT=Systemic Anti-Cancer Therapy
Source: Company response to clarification question C3

Walton Oaks, Dorking
Road, Tadworth KT20 7NS

Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Dear Ross,

Re: ID6289 Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer - Additional Information Request

Thank you for the clarification questions – Pfizer is grateful for the opportunity to submit further evidence for the above appraisal. Responses to the additional requests below. If you do require any further clarification, please do not hesitate to reach out

Your sincerely,

[redacted]
For and on behalf of Pfizer UK

Response to additional information request

1. **Please could you provide an explanation for the difference between the median overall survival for crizotinib in the SACT dataset (21.9 months, 95% CI: 17.7 to 29) compared to the PROFILE 1001 trial (51.4 months, 95% CI: 29.3 to not estimable [NE])?**

The difference in the median overall survival (OS) between the SACT dataset and PROFILE 1001 trial can be explained by the difference in patient characteristics between the two sources of evidence. The inclusion criteria of PROFILE 1001 permitted participants to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with participants with an ECOG PS of 2 only allowed upon agreement between the investigator and sponsor (of which there was only 1 patient).[1] However, patients eligible for crizotinib via the Cancer Drugs Fund (CDF) could have an ECOG PS from 0-2. Additionally, the crizotinib CDF appraisal year four report showed patients with PS 3 also received crizotinib. Therefore patients presenting with a worse health profile have been included in the SACT RWE.[2] Additionally, the PROFILE 1001 trial defined a specific inclusion/exclusion criteria which selected for medically fit patients, whereas the criteria for use of crizotinib in the CDF represented a real world population. This suggests that patients with other comorbidities (and thus a worse health profile) may have also been included in the SACT RWE. In addition, the CNS metastasis rate in both PROFILE 1001 and SACT dataset is not reported and therefore it's not possible to determine if this is a key variable in the outcomes of overall survival.

On average, patients in the SACT RWE dataset were older compared to patients in the PROFILE 1001 trial (median age: 63 years vs. 55 years, respectively), which can determine relative survival rates due to the strong inverse correlation between age and cancer survival.[3,4] The SACT data set also had a larger proportion of patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 compared to the PROFILE 1001 trial (26.4% vs. 1.9%, respectively), showing a higher proportion of patients in the SACT dataset with greater limitations in daily living abilities due to disease severity, wellbeing and more specifically a significantly higher proportion of patients with a greater likelihood of progressing to ECOG grade of 5 (i.e. dead).[1,5]

In addition to the difference in patient characteristics, there were also differences in the median trial follow-up in the SACT dataset which was significantly shorter compared to the PROFILE 1001 trial (17.4 months vs. 62.6 months, respectively), therefore restricting the median progression-free and overall survival for data collected in the RWE dataset.[1,5]

EAG comment

The company has reported that 26.4% of SACT patients had an ECOG PS ≥2. However, data provided in the SACT 2022 report (Table 4) show that, of the 116 patients for whom ECOG PS was reported, 18 patients had an ECOG PS ≥2, i.e., 16%. This means that differences in ECOG PS are unlikely to fully explain differences in SACT and PROFILE 1001 trial outcomes.

The EAG considers that the response provided by the company does not fully explain differences in outcomes between NHS and PROFILE 1001 trial patients and the generalisability of PROFILE 1001 trial results to NHS patients remains uncertain.

2. Please could you explain the rationale for calculating time-varying HRs rather than constant HRs for the STC?

The rationale for calculating time-varying HRs pertains to the proportional hazards assumptions not strictly holding for any of the time to event outcomes. This is can be seen from Figure 5 for progression-free survival (PFS) (CS, Appendix D 2.3.1), Figure 10 for OS (CS, Appendix D 2.3.2) and Figure 15 for Duration of response (DoR) (CS, Appendix D 2.3.5) where the Kaplan-Meier (K-M) curves for crizotinib and Entrectinib are crossing.

EAG comment

In the EAG still considers that as the PH assumption was not violated, it would have been appropriate to carry out STCs that assumed constant hazards.

3. Please could you provide an additional analysis calculating constant HRs for the STC?

The methodology employed to estimate the constant hazard ratios (HRs) for OS, PFS and DoR, between crizotinib and Entrectinib utilises the Simulated Treatment Comparison (STC) unanchored approach. The method integrates the individual patient data (IPD) from crizotinib trials (PROFILE1001 and OxOnc) with aggregated data (AGD) from Entrectinib trials (ALKA-372-001, STARTRK-1, and STARTRK-2). Initially, the IPD for crizotinib is processed by renaming and transforming variables to ensure comparability, including categorisation of performance status, smoking status, and other relevant factors. For Entrectinib, where only aggregated baseline characteristics and K-M curves are available, pseudo-IPD is generated based on these sources. These datasets are subsequently combined to form a combined dataset, incorporating key covariates for analysis.

This analysis employs the semi-parametric Cox proportional hazards regression model to estimate the effect of crizotinib relative to entrectinib on OS, PFS, and DoR. The model assumes that hazard ratios between groups remain proportional over time, an assumption referred to as proportional hazards.[6] This implies that while the absolute risk may change over time, the ratio of hazards between the groups remains constant.[6]

The Cox model is adjusted for baseline characteristics, with covariates centred at their mean aggregated data values to align patient populations across treatments. Similarly to the time-varying approach, two models were developed: a base case model, which adjusts for age, smoking status, and ECOG performance status, and a sensitivity model, which includes additional covariates such as ethnicity, sex, and histological classification. Entrectinib is set as the reference treatment, and the hazard ratio (HR) for crizotinib is calculated along with 95% confidence intervals to account for uncertainty (see Table 1). The constant HR results follow the same pattern as those obtained from the time-varying approach in terms of direction and magnitude, as there is significant overlap in the 95% confidence intervals of the

respective estimates. We believe that this provides supporting evidence that entrectinib and crizotinib have similar clinical effect and supports the cost comparison approach.

Table 1: Summary of Cox Proportional Hazards Model Results and averaged time-varying HR for OS, PFS, and DoR

Outcome	Constant HR [95% CI] Cox Proportional model	Average HR [95% CI] Time-varying approach
OS (base case)	[redacted]	[redacted]
OS (sensitivity)	[redacted]	
PFS (base case)	[redacted]	[redacted]
PFS (sensitivity	[redacted]	
DOR (base case)	[redacted]	[redacted]
DOR (sensitivity)	[redacted]	

CI: confidence interval, DoR: duration of response, HR: hazard ratio, OS: overall survival, PFS: progression-free survival

EAG comment

The company constant HRs are in line with the company average time-varying HRs; however, the width of the 95% CIs around estimated treatment effects, particularly for OS, reflect a large amount of uncertainty.

4. Please could you provide additional analyses where line of treatment and presence of brain metastasis are adjusted for?

Line of therapy

In both the base case and sensitivity models, additional analyses were performed to adjust for prior line of treatment (0, 1, ≥2). The models with this additional adjustment were limited to using individual participant data from the OxOnc trial, as data from the PROFILE 1001trial is not available for this variable. This limitation should be considered when interpreting the results, as the analysis reflects a subset of the patient population in the STC (see Table 2 and Table 3). The results are very similar between the two approaches, in addition to the comparison of results not adjusting for prior line of treatment (Column 'Not adjusted for treatment line (OxOnc trial)') across all three time-to-event outcomes, suggesting that this potential adjustment does not significantly impact the results.

Table 2 Summary of Cox Proportional Hazards Model and averaged time-varying HR results for OS, PFS, and DoR (OxOnc population)

	Additional adjustment on treatment line (OxOnc trial)		Not adjusted for treatment line (OxOnc trial)
+/Outcome	Constant HR [95% CI] Cox Proportional model	Average HR [95% CI] Time-varying approach	Average HR [95% CI] Time-varying approach
OS (base case)	[redacted]	[redacted]	[redacted]
OS (sensitivity)			
PFS (base case)		[redacted]	[redacted]
PFS (sensitivity	[redacted]		
DOR (base case)		[redacted]	[redacted]

DOR (sensitivity)	[redacted]		

Table 3 Summary of logistic regression model results for ORR (OxOnc population)

Outcome	OR [95% CI] Additional adjustment on treatment line	OR [95% CI] No additional adjustment on treatment line
ORR (base case)	[redacted]	[redacted]
ORR (sensitivity)	[redacted]	[redacted]

EAG comment

ITC results adjusted for line of treatment are consistent with the STC constant HR and time-varying HR results that were not adjusted for line of treatment. However, the EAG considers that all HR results are uncertain (wide confidence intervals).

Brain metastases

Regarding brain metastases, it was not possible to adjust for this variable in either the base case or sensitivity models due to the very small number of patients who presented with brain metastases at baseline (no reported value vs. 18.1%, in the PROFILE 1001 and OxOnc trials, respectively). The limited occurrence of this condition reduces the statistical power to make reliable inferences on its impact within the adjusted models. As such, any potential effects of brain metastases on the outcomes have not been accounted for in these analyses.

EAG comment

The EAG agrees with the company that it was not possible to adjust for brain metastases at baseline (EAR, p45).

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