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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

ENTRECTINIB (ROZLYTREK)

(Hoffmann-La Roche Ltd.)

Indication: For the first-line treatment of patients with ROS1 positive locally advanced or metastatic non-small cell lung cancer.

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Abbreviations

AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
APT	All Patients Treated
ASCO	American Society of Clinical Oncology
BICR	Blinded Independent Review Committee
BM	Brain Metastases
BOR	Best Overall Response
BR	Best Response
BSA	Body Surface Area
CBR	Clinical Benefit Rate
CCO	Cancer Care Ontario
CGP	Clinical Guidance Panel
CHF	Coronary Heart Failure
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CROS	Canadian ROS
CRR	Complete Response Rate
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
DAC	Drug Advisory Committee
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicities
DOR	Duration of Response
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
ECOG QLQ-C30	Eastern Cooperative Oncology Group Quality Of Life Questionnaire Of Cancer Patients
EIAED	Enzyme-Inducing Anti-Epileptic Drug
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC *QLQ-LC13*	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module
EQ-5D	EuroQoL 5-Dimension
ESMO	European Society for Medical Oncology
FDA	Federal Drug Administration
FISH	Fluorescence in Situ Hybridization
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
HCC	Hepatocellular Carcinoma
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HrQoL	Health Related Quality of Life
IC-DOR	Intracranial Duration of Response
IC-ORR	*Intracranial Objective Response Rate*
IC-PFS	Intracranial Progression Free Survival
ICI	Immune Checkpoint Inhibitors
IEA	Integrated Efficacy Analysis
IHC	Immunohistochemistry
IPD	Individual Patient Data
IQR	Interquartile Range
ITC	Indirect Treatment Comparison
LCC	Lung Cancer Canada
MAIC	Matched Adjusted Indirect Comparisons
MBq	Megabecquerel
MI	Myocardial Infarction

MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Estimable
NED	No Evidence of Disease
NGS	Next Generation Sequencing
NOC	Notice of Compliance
NR	Not Reported
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophic Tyrosine Receptor Kinase
ORR	Objective Response Rate
OS	Overall Survival
PAG	Provincial Advisory Group
pCODR	Pan-Canadian Oncology Drug Review
PD	Progressive Disease/ Pharmacodynamics
pERC	pCODR Expert Review Committee
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
QD	Once a Day
RANO	Response Assessment in Neuro-Oncology
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
ROS1	Receptor Tyrosine Kinase
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease/ Standard Deviation
SIRT	Selective Internal Radiotherapy

SMD	Standard Mean Difference
SNP	Single-Nucleotide Polymorphism
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TRK	Tyrosine Kinase.
VAS	Visual Analogue Scale

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding entrectinib (Rozlytrek) for ROS-1- positive advanced non-small cell lung cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of entrectinib (Rozlytrek) for the first-line treatment of patients with ROS-1 positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

Entrectinib is a selective inhibitor of the receptor tropomyosin protein kinases TRK A/B/C, c-ros oncogene 1 (ROS-1), and anaplastic lymphoma kinase (ALK). Health Canada has issued market authorization, without conditions, for entrectinib for the treatment of patients with ROS-1 positive locally advanced or metastatic NSCLC not previously treated with crizotinib. Entrectinib has the following CADTH reimbursement criteria: entrectinib as monotherapy for the first-line treatment of patients with ROS-1 positive locally advanced or metastatic non-small cell lung cancer. Note that the Health Canada indication differs from the reimbursement criteria, in that it specifies ‘not previously treated with crizotinib’ in its indication.

The Health Canada recommended dose is 600 mg administered orally, once daily. It is recommended that patients are treated with entrectinib until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Systematic Review Evidence

Three trials met the inclusion criteria for the systematic review. ALKA-372-001 was an open-label, single group, multicenter phase 1 dose escalation study examining entrectinib monotherapy administered orally as capsules in the 3 dosing schedules (detailed in Table 8) until recommended phase 2 dose (RP2D) determination (doses ranged from 100-1600 mg/m^2). STARTRK-1 was a multicentre, open-label, single-arm, phase 2 basket study examining entrectinib monotherapy dose (capsules taken orally) of 100 mg/m2 once daily, in fed condition, for 28 consecutive days in repeated 4-week cycles (other doses tested: 200 mg/m2, 400 mg/m2, or 600 or 800 mg once daily). STARTRK-2 was a multicentre, open-label, single-arm, phase 2 basket study examining entrectinib monotherapy administered orally as capsules at a dose of 600 mg per day continuously for 28 days (4-week cycles).

The integrated data to support efficacy were derived from a pooled subgroup of patients with locally advanced or metastatic ROS-1 positive NSCLC from the three trials (ALKA-372-001, STARTRK-1 and STARTRK-2) with a pre-specified final clinical data cut-off date of May 31, 2018 and updated results provided at the October 31, 2018 and May 1, 2019 data cut-off dates. This primary Efficacy-Evaluable Analysis Set (n = 53) consisted of patients enrolled up to April 30, 2017 with a clinical cut-off date of May 31, 2018. Additional updated analyses were performed for a pooled subgroup of 94 patients with ROS-1 positive NSCLC with measurable disease enrolled up to November 30, 2017. This subgroup (n = 94) consisted of the 53 patients in the ROS-1 NSCLC Efficacy Evaluable Analysis Set plus 41 ROS-1 NSCLC patients, who at the time of the updated data cut-off date of May 1, 2019, all

had >12 months of follow-up. The trials were conducted in Italy (ALKA), US, Spain, and South Korea (STARTRK-1), and 15 countries globally (STARTRK-2) - of note, none were conducted in Canada. Safety data were analyzed at the final data cut-off date (May 31, 2018) and updated at the October 31, 2018 data cut-off date. Safety data were presented in two sets: 1) all patients (N = 355; May 31, 2018 and N = 504; Oct 31, 2018) (regardless of tumour type or gene rearrangement) enrolled and treated with at least one dose of entrectinib in three adults trials (ALKA-372-001, STARTRK-1 and STARTRK-2) and supplemented with few patients from one pediatric trial (STARTRK-NG) and 2) all patients (n = 134; May 31, 2018 and N = 210; October 31, 2018) in the safety set that had ROS-1-postive NSCLC and received at least one dose of entrectinib. Safety data were pooled for 357 patients (2 were eventually excluded because they did not receive entrectinib, resulting in 355 patients). The safety data was not updated to align with the latest May 1, 2019 clinical data provided.

The Primary ROS-1 positive NSCLC Efficacy-Evaluable Population (n = 53) was the primary efficacy population for this CADTH submission. It consisted of a pooled subgroup of 53 adult patients ≥18 years of age with ROS-1 positive NSCLC who received at least one dose of entrectinib (600 mg), had at least 12 months of follow-up from the time of first response by blinded independent committee review (BICR) assessment, had measurable disease at baseline (as per RECIST version 1.1), had not previously received a ROS-1 inhibitor (e.g., crizotinib), and had Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤2. There were nine patients from the ALKA trial, seven patients from the STARTRK-1 trial, and 37 patients from the STARTRK-2 trial included in this data set.

The Primary ROS-1 Efficacy Evaluable Analysis Set comprised of 34 (64%) female and 19 (36%) males at baseline. The median age was 53 (range 27-73), with a large proportion of patients <65 years of age (n = 42; 79.2%). This population included 23 patients (43.4%) that had metastatic CNS disease. Most patients were White (n = 31; 59%) followed by Asian (n = 19; 35.8%), and Black/African American (n = 3; 5.7%). Most patients had an ECOG PS of 1 (n = 27; 51%) or 0 (n = 20; 38%) and a minority of patients were ECOG PS of 2 (n = 6; 11%). There were 22 (42%) patients with a history of smoking; whereas just over half of patients (n = 31; 59%) did not have a smoking history. The number of previous systemic therapies received by patients were reported [n(%)] (0: n = 14 (26.4%), 1: n = 25 (47.2%), 2: n = 6 (11.3%), 3: n = 3 (5.7%), 4: n = 3 (5.7%), >4: n = 2 (3.8%). Most patients (86.8%) had received previous anticancer therapy prior to enrollment across three studies. Chemotherapy was the most common (79.2%), followed by non-ROS-1 targeted therapy (17.0%), immunotherapy (9.4%) and hormonal therapy (1.9%). Furthermore, 45.3% received previous radiotherapy and 52.8% had previous surgeries. The targeted therapies that were received by 9 patients included erlotinib (n = 5), gefitinib (n = 1), nintedanib (n = 1), and crizotinib (n = 2).

Sex, ethnicity, and ECOG PS of the ROS-1 Integrated Efficacy Evaluable Analysis Set (n = 53) was largely consistent with the overall Safety Analysis Population (n = 355). The patient characteristics of the Safety Analysis Population (n = 355) were as follows: median age of 55 years (range: 4 to 86), 55% were female, 66% were White, 23% were Asian, 4.5% were Black or African American, and 5% did not report their race. In addition, 91% had an ECOG PS of 0 or 1. Most adult patients had no history of smoking (57.2%,183/320) with the remaining 42.8% (137/320) being current or previous smokers.

The primary efficacy outcomes for the integrated efficacy set were objective response rate (ORR), best overall response (BOR) and duration of response (DOR) as per BICR assessment. Secondary outcomes were clinical benefit rate (CBR), progression-free survival (PFS), time-to-CNS progression, overall survival (OS), intracranial objective response rate (IC-ORR), intracranial duration of response (IC-DOR), and intracranial PFS (IC-PFS). An exploratory outcome was ORR as per investigator. Health-related Quality of Life (HRQoL) data were only collected in the STARTRK-2 trial, as secondary outcomes, via self-administered questionnaires. The instruments used to assess the patient reported outcomes included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EORTC Lung Cancer module (QLQ-LC13) and the EuroQoL Group EQ-5D.

Table 1 summarizes the key outcomes for the integrated analysis. The median duration of follow-up was 15.5 months (interquartile range [IQR] was 13.4 months to 20.2 months). The primary outcome, ORR, was 77% (64-88%), with three patients (6%) experiencing a complete response (CR) and 38 (72%) experiencing a partial response (PR). The duration of response (DOR) was a median of 24.6 months (95% CI: 11.4-34.8) and PFS was a median of 19.0 months (95% CI: 12.2-36.6). Median OS was not reached as of May 31, 2018. Efficacy results from later data cut-offs dates were overall consistent with the results from the May 31, 2018 data cut-off date.

HRQoL was only evaluated in the STARTRK-2 trial. Patient reported outcomes data were descriptively analyzed at the May 31, 2018 and May 1, 2019 data cut-off dates. HRQoL results were overall consistent between data cut-off dates. Due to the small number of patients (n = 37) available at the May 31, 2018 data cut, this report focuses on the results from the May 1, 2019 data cut-off date with 78 patients providing HRQoL data. For the May 1, 2019 data cut-off date, all patients in the expanded ROS-1 Efficacy Evaluable Analysis Set from STARTRK-2 (n = 78) completed at least one question in the EORTC QLQ-C30 questionnaire and all except one patient completed at least one question in the QLQ-LC13 instruments. The number of patients available to provide patient-reported outcomes data declined gradually over the course of the study. Interpretation of changes from baseline is limited by the high patient drop-off at later cycles. At baseline, the Global Health Status/QoL and Functional Scale scores were moderate-to -high and showed higher values compared to the base line value (higher scores reflecting improvement) at most assessment points, except the cognitive functioning scale which showed worsening scores at most assessment points. For the QLQ-LC13 instrument, patients reported lung symptom burden at baseline with trends towards improvement. Results were also provided by the sponsor for the EQ-5D Visual Analogue Scale (VAS) based on a larger sample (n = 145) with ROS-1 positive patients from the STARTRK-2 trial. The exact criteria for defining the 145 patients were not provided. Scores generally increased and showed improvements over the course of the treatment. The mean changes from baseline were not provided for the EQ-5D VAS.

In the n = 355 set, almost all patients (99%) experienced at least one AE. AEs of any Grade occurring most frequently included fatigue (48%), constipation (46%), dysgeusia (44%), dizziness (38%), edema (40%), diarrhea (35%), nausea (34%), dysesthesia (34%), dyspnea (30%), cough (24%), cognitive impairment (27%), peripheral sensory neuropathy and headache (18% each), ataxia (17%) and mood disorders (10%). The majority of patients (61%) experienced AEs of Grade 3 or 4. AEs of Grade 3 or 4 occurring most frequently included anemia (9%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), pneumonia, pulmonary embolism, hypoxia, and AST increased (each 3.4%), cognitive impairment (4.5%), pleural effusion and AST increased (each 3.1%), hypotension/orthostatic hypotension and hypophosphatemia (each 2.8%), neutropenia and syncope (each 2.5%), UTI (2.3%), diarrhea, hypokalemia, hyponatremia, and lipase increased (2.0%). Serious AEs occurred in 39% of patients. A total of 99% of patients experienced treatment-related AEs and 9% experienced treatment related serious AEs. AEs leading to discontinuation occurred in 9%, whereas 28% experienced an AE leading to dose reduction and 46% experienced an AE leading to drug interruption. Six percent of patients experienced an AE leading to death.

Limitations:

- All trials were single arm and did not include a comparator, making it unclear whether patients will have better or worse outcomes with entrectinib when compared to the most relevant current treatment options for their tumor type.
- The results of three open-label, single arm trials (ALKA, STARTRK-1 and STARTRK-2) were pooled to form the ROS-1 NSCLC Efficacy Evaluable Analysis Set. There were differences with regards to study designs and outcome definitions. The approach to combine these trials without any adjustments for heterogeneity may introduce biases into the results. The sponsor noted that because of the rare disease setting for ROS-1 positive NSCLC, both the FDA and EMA agreed with the approach to pool efficacy and safety data from the clinical studies (ALKA, STARTRK-1, and STARTRK-2).
- Formal statistical significance and hypothesis testing was not performed. Point estimates with 95% CIs were reported to estimate the magnitude of treatment effect. No statistical adjustments for multiplicity were made due to the rarity of the patient population and expectation of significant clinical benefit; and no statistical adjustments were made to account for subgroup effects associated with the pooling of data for integrated analysis.
- Interpretation of time-to-event endpoints such as OS or PFS is limited in single-arm studies. As noted in the FDA Guidance for Industry[1], because of variability in the natural history of many forms of cancer, a randomized trial is required to evaluate time-to-event endpoints.
- Limited interpretation of safety data: Due to the non-comparative nature of the analyses it is not possible to clearly determine if symptoms are related to the underlying malignancy or to entrectinib-related adverse events.
- Limited interpretation of HRQoL data: HRQoL data were summarized descriptively. The number of patients for whom PRO data were available steadily declined over the course of the study which limits the interpretation of the results especially at later cycles (Cycle 23; only 18 patients out of 78 patients provided patient-reported outcomes data). Additionally, the trial was non-randomized and the impact of entrectinib in relation to other therapies is unknown.

Table 1: Highlights of Key Outcomes

	Integrated Analysis (Entrectinib 600 mg)
Data cut-off date (primary)	May 31, 2018
Median duration of follow-up, Months	15.5 months (IQR 13.4–20.2)
Primary Outcome	
ORR, n; % (95% CI)	41; 77% (64-88%)
Key Secondary Outcomes	
DOR, median in months (95% CI)	24.6 (11.4-34.8)
PFS, median in months (95% CI)	19.0 (12.2-36.6)
OS, median in months (95% CI)	NE (NE, NE)
Patients with OS event (%)	9 (17)
Harms Outcome, (%)	**Integrated Safety Population (N = 355)**
Updated data cut-off date	**October 31, 2018**
Grade ≥3	64
AE (any grade)	99
TRAE	92
WDAE	9
SAE	42
TRSAE	9
AE leading to dose reduction	28
AE leading to dose interruption	46
AE leading to death	6

AE = adverse event; CI = confidence interval; DOR = duration of response; HR = hazard ratio, HRQoL = health-related quality of life, IQR = interquartile range; NE = not estimable; ORR = objective response rate; PFS = progression-free survival; SAE = serious adverse events; SD = standard deviation; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event; WDAE = withdrawal due to adverse event

Source: Drilon et al, (2020)[2], Sponsor's submission[3]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Lung Cancer Canada (LCC) provided input on entrectinib (Rozlytrek) as a monotherapy for the first-line treatment of patients with ROS-1 positive locally advanced or metastatic NSCLC.

LCC highlighted that ROS-1 positive NSCLC patients have limited options. Crizotinib is the agreed upon standard of care; however, it is not funded in Canada and is not affordable. Alternative options include chemotherapy, which is associated with significant side effects and multiple, long hospital trips for administration. Additionally, time taken off of work to address the needs associated with chemotherapy is particularly substantial for this population as patients tend to be younger; thus, handling financial hardships, competing family priorities, and care related to the disease and treatment results in a significant physical and psychological burden for the patient and caregiver. Immunotherapy is another option, which has more manageable side effects but has been shown to work poorly in ROS-1 positive NSCLC patients regardless of PD-L1 status. LCC stated that Canadians have a higher disease burden compared to the rest of the world due to the limited access to oral therapies that are more effective than chemotherapy and allow for a higher quality of life.

Regarding treatment expectations, patients value treatment efficacy; treatment convenience; more manageable side effects; and treatment outcomes such as improved symptoms, quality of life, and survival rates or maintaining a progression-free state.

Entrectinib being an oral medication would improve treatment convenience as this method of delivery lessens a significant amount of stress and dependency on caregivers by reducing the need for multiple, long hospital visits for intravenous administration. Patients also hope to access entrectinib as it could address the unmet need of treating CNS metastases since entrectinib has been demonstrated to have better blood-brain barrier penetration compared to crizotinib.

Among those with treatment experience, entrectinib was summarized to control the cancer; elicit manageable side effects; improve treatment experience due to the feasible administration; and allow patients to enjoy life activities, remain independent, live a new normal, and for some patients to return to work. Namely, among the 16 responses gathered by the LCC, seven patients had a duration of response of more than 19 months and two patients had no evidence of disease. The side effects associated with entrectinib were reported by most patients to be manageable. Edema or weight gain followed by taste changes and fatigue were the most commonly reported side effects. The oral administration of entrectinib improved treatment experience as patients were able to take their medication at home and there was a reduced need for injections and long hospital visits or stays. Patients reported feeling less tired after treatment and could attend appointments on their own, which alleviated the burden on caregivers. Moreover, entrectinib allowed some patients to achieve a high level of functionality to return to work, which is important for NSCLC patients who are typically younger. Overall, entrectinib has allowed patients to enjoy life activities, stay active, try new activities, remain independent, and live a new normal.

Ultimately, LCC specified that the goal of cancer treatment is to provide the right drug for the right target and person. Notably, entrectinib not only personalizes the treatment but also addresses CNS presentations and allows patients to live well, achieve new life milestones, and spend more time with family and loved ones. There are a number of approved targeted forms of treatment for other molecular driven cancers such as EGFR and ALK NSCLC; thus, patients with the ROS-1 mutation should also be given the same opportunities. Additionally, with the likelihood of CNS involvement at diagnosis or post-treatment, which is a frequent cause of morbidity and mortality, entrectinib is a viable option that addresses this need. First-line crizotinib is currently still in pricing negotiations and studies have shown that it may not penetrate the blood brain barrier. The LCC also mentioned the unlikelihood of a phase III trial being conducted soon; accordingly, they ask that a conditional approval be granted as this would allow the collection of third-line data while providing access to patients and to allow for the collection of real-world evidence.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing of treatment and place in therapy for entrectinib

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities
- Number of patients requiring and access to ROS-1 testing

Registered Clinician Input

A total of two registered clinician inputs were provided for the review of entrectinib (Rozlytrek) for the first-line treatment of adult patients with ROS-1 positive locally advanced or metastatic NSCLC: two clinicians provided input on behalf of Cancer Care Ontario (CCO) Lung Drug Advisory Committee (DAC) and six clinicians provided input on behalf of LCC. Overall, it was noted that entrectinib is an orally administered targeted therapy that demonstrates superior tolerability and effectiveness compared to chemotherapy and immunotherapy, which are the current treatment options for ROS-1 NSCLC. Namely, chemotherapy is contraindicated in poor performance status patients (e.g., frailer patients, patients with co-morbidities, or patients with CNS metastases) while immunotherapy has limited activity in tumours harbouring driver mutations (e.g., ROS-1, EGFR, and ALK) and exhibit a potential for

significant autoimmune toxicities. As entrectinib is a selective TKI inhibitor, a companion diagnostic test is required to identify ROS-1 rearrangements; this test is currently not funded in Ontario and is variably implemented across Canada. The LCC clinicians highlighted that entrectinib would address the clinical unmet need for all ROS-1 tumour types, not exclusively for NSCLC, including less common ROS-1 rearrangements in glioblastoma multiforme; cholangiocarcinomas; and colorectal, gastric, and ovarian cancers. Moreover, the CCO clinicians stated that it would be extremely rare for patients to have both ROS-1 and NTRK mutations as the TRK fusions are already so rare, and the LCC clinicians stated that it is generally felt that these genetic aberrations are mutually exclusive.

Both inputs supported up-front administration of targeted therapy (entrectinib or crizotinib) followed by chemotherapy then immunotherapy (PD-1 inhibitors); the CCO clinicians specified that entrectinib should be the first TKI a patient receives and not necessarily as first-line treatment (i.e. patients may receive treatment prior to determining ROS-1 status). Accordingly, the clinicians supported the practice of switching to entrectinib from chemotherapy upon confirmation of a patient's ROS-1 re-arrangement status. Moreover, the clinicians felt that entrectinib is either as effective or slightly more effective than crizotinib; however, no robust direct comparison exists (e.g. randomized controlled trial [RCT]). Notably, direct comparisons may not be possible due to the rarity of ROS-1 gene re-arrangements. Nevertheless, both inputs specified that crizotinib is less CNS-penetrant than entrectinib; therefore, entrectinib would be preferred for patients with CNS metastases. However, it was noted that there is no direct evidence to inform the use of entrectinib in ROS-1 positive NSCLC patients who experience CNS disease progression on crizotinib. Additionally, both inputs indicated that there is no strong evidence to support the use of PD-1 or PD-L1 inhibitors following entrectinib; although, the LCC clinicians stated that immunotherapy could be considered after entrectinib, other ROS-1 inhibitors, and chemotherapy since ROS-1 patients were not excluded from immunotherapy trials unlike EGFR- and ALK positive patients. Further, when asked if patients with ROS-1 mutations can be given first line pembrolizumab if their tumour exhibits high PD-L1 expression, all clinicians indicated a preference for targeted agents over immunotherapy. Of note, the CCO clinicians specified that, it is difficult to determine optimal sequencing for ROS-1 positive NSCLC since the supporting data for sequencing is in TKI naïve patients.

Overall, the clinicians noted that entrectinib may address the clinical unmet need for more tolerable and effective therapies for ROS-1 positive NSCLC; namely, the need for a CNS-penetrant and effective agent. Thus, both inputs expressed support for making entrectinib available to facilitate access to multiple treatment options for ROS-1 positive NSCLC. The LCC clinicians specified that entrectinib should be made available since multiple EGFR inhibitors have been approved (e.g., gefitinib, afatinib, dacomitinib, and osimertinib); thus, ROS-1 positive NSCLC patients should have access to targeted therapies for ROS-1 mutations as well. Additionally, they highlighted that entrectinib should be available despite the recent conditional positive recommendation of crizotinib because it is common for patients to develop side effects to targeted agents. Thus, the availability of entrectinib as a second targeted option is particularly advantageous since it may be also used to treat primary brain tumours and brain metastases.

Summary of Supplemental Questions

Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison Using Matched Adjusted Indirect Comparison

The available clinical trials of entrectinib did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor provided indirect treatment comparisons (ITCs) using matched adjusted indirect comparisons (MAICs) of the relevant comparators, which were identified based on a systematic review of treatments for NSCLC. The objective of the MAICs was to estimate the relative treatment effects of entrectinib compared with the following: 1) crizotinib (based on the PROFILE 1001 study and pooled PROFILE 1001/Wu 2018 studies—for the PFS outcome only), 2) pemetrexed plus platinum followed by pemetrexed maintenance (based on the ASCEND-4 study), and 3) chemotherapy (based on the PROFILE 1007 study) for patients with advanced or metastatic ROS-1 NSCLC in the first- or second-line setting.

The ITCs performed included MAIC analyses to derive comparative estimates for the outcomes of OS, PFS, ORR, and discontinuation due to AEs. The methods and results of the ITCs were critically appraised by the CADTH Methods Team according to best practice principles for MAICs. For entrectinib versus crizotinib, the results were not statistically significant across all outcomes (based on PROFILE 1001 and the pooled PFS results for PROFILE 1001 and Wu 2018). For entrectinib versus chemotherapy, the results were statistically significantly in favour of entrectinib for OS, PFS, and ORR (based on PROFILE 1007). No statistically significant differences were observed for discontinuation due to AEs. For entrectinib versus pemetrexed/platinum, the results were statistically significantly in favour of entrectinib for OS, PFS, and ORR (based on ASCEND-4). No statistically significant differences

were observed for discontinuation due to AEs. The CADTH Methods Team concluded the ITC results should be interpreted with extreme caution considering several limitations associated with the analyses, such as substantial heterogeneity between studies, inability to adjust for all potential confounders and prognostic variables, and use of inappropriate analysis methods for MAIC. Overall, due to the limitations identified, the findings from the MAIC were inconclusive because the assumptions used for the unanchored analyses are impossible to meet and present an unknown amount of bias in the unanchored estimate.

See section 7.1 for more information.

Critical Appraisal of the Sponsor-Submitted Propensity Score Analysis Using Real-World Data

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor supplied a propensity score analysis using real-world data from the Flatiron Health Analytic Database. The objective of the propensity score analysis was for the comparative analysis between crizotinib and entrectinib among ROS-1 NSCLC patients for time to treatment discontinuation (primary outcome), OS, and PFS (secondary outcomes).

Data on crizotinib came from electronic health records from multiple sources in the United States. Propensity score matching was used to derive comparative estimates for the time to treatment discontinuation, PFS, and OS between patients treated with entrectinib and crizotinib. The patients in the crizotinib study were propensity score matched to patients in the entrectinib integrated analysis on the following variables: gender, race, age, smoking history, brain metastases, and prior line of therapy. The propensity score matching process increased the effective sample size from 69 to 78 patients in the crizotinib arm. The propensity score analysis produced an HR of 0.68 (95% CI: 0.47, 0.98) favouring entrectinib over crizotinib for treatment discontinuation. For PFS, the HR was 0.51 (95% CI: 0.34, 0.75), which also suggests that entrectinib is favoured over crizotinib in the propensity score analysis. The OS results also favoured entrectinib over crizotinib (HR 0.39, 95% CI: 0.23, 0.65). The pCODR Methods Team concluded that the results from the propensity score matching analyses should be interpreted with extreme caution considering several limitations. The most significant of these limitations included 1) one arm came from a real-world data study and the other from a trial; therefore, the propensity score method may not address differences in study designs and 2) the omission of important variables from the matching process, which may confound the treatment effect estimates obtained. The treatment effect estimates obtained in the propensity score analysis are likely biased and not solely due to the effects of the treatments examined, and therefore, should be interpreted with extreme caution.

See section 7.2 for more information

Comparison with Other Literature

The sponsor included treatment estimates for crizotinib versus pemetrexed-plus-platinum chemotherapy from the PROFILE 1014 trial[4] in the Pharmacoeconomic (PE) model to help inform cost-effectiveness estimates for entrectinib. PROFILE 1014 was a randomized, open-label, phase 3, international trial comparing crizotinib (n = 172 patients) with pemetrexed-plus-platinum chemotherapy (n = 171 patients). Patients were included if they had ALK positive NSCLC and did not receive previous systemic treatment; however, patients with treated brain metastases were included if they were neurologically stable for at least two weeks prior to enrollment and did not require ongoing glucocorticoid treatment. Additional criteria were age 18 years and above, measurable disease as per RECIST version 1.1, ECOG PS 0 to 2, and adequate hepatic/renal/bone marrow function. Patients were randomized to either 250 mg twice daily oral crizotinib or intravenous pemetrexed (500 mg per square meter of body-surface area) plus either cisplatin (75 mg per square meter) or carboplatin (target area under the curve of 5 to 6 mg per milliliter per minute) every three weeks up to a maximum of six cycles. If safety screening criteria were met, patients could cross over to crizotinib if disease progression was confirmed by independent radiologic review. There was a median duration of OS follow-up of 17.4 months in the crizotinib arm versus 16.7 months in the chemotherapy arm. For OS, the results favoured crizotinib with a HR of 0.82 (95% CI: 0.54,1.26), which was consistent with the PFS results (HR of 0.45, 95% CI: 0.35, 0.60).

Notably, directly using the HR as reported in the PROFILE 1014 trial as the comparative estimate in the economic analysis is a major limitation as it is not possible to determine if any observed differences in efficacy between the therapies is solely due to the treatment or, rather, due to bias or confounding factors such as differences in study populations, definitions of outcomes, or study designs. The opposite may also occur where a finding of similar efficacy between treatments may be incorrect because differences in the included

trials may have masked true treatment differences.[5] Due to the above limitations, the comparative efficacy estimates obtained should be interpreted with caution as they are likely biased. It is difficult to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with entrectinib compared with pemetrexed-plus-platinum chemotherapy in the economic analysis.

See section 8 for more information.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for entrectinib for ROS-1 positive locally advanced or metastatic NSCLC

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Enrollment via molecular testing	Patients in the integrated efficacy analysis (n = 53) were enrolled through a variation of molecular tests: • FISH (n = 15) • NGS (n = 36)	Are there any known differences between the testing methods that would impact the clinical outcomes, or the resources used to achieve the outcomes?	The CGP noted that the molecular tests used, such as immunohistochemistry (IHC) followed by confirmation test with fluorescence in situ hybridization (FISH) or NGS seem reasonable and are valid tests in Canadian clinical practice. Both NGS and FISH tests are looking for fusion (s) at the DNA or RNA level. There would be no impact on outcomes of method of detection. The resources would be quite high if universal FISH testing were done, but the evolving standard for lung cancer is multiplex testing using NGS of multiple mutations (EGFR/ALK/ROS/RET/B-RAF etc.)
	Oran dysfunction	Patients in the integrated efficacy analysis had to have adequate organ function	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?	Given the generally tolerable safety profile of entrectinib, the CGP suggests it is up to the discretion of the treating physician to apply some flexibility in terms of using entrectinib in patients with slightly lower lab parameters/organ dysfunction.
Outcomes	Appropriateness of Primary and Secondary Outcomes	The primary endpoint of the integrated analysis was ORR and DOR determined by BICR (prospectively for patients from STARTRK-2 and retrospectively for patients from ALKA or STARTRK-1).	Does the selection on outcomes limit the interpretation of the trial results with respect to the target population?	ORR is a clinically relevant endpoint as both an anticipated surrogate for OS, and as an endpoint in itself in improving disease related symptoms such as cough, pain, shortness of breath, and fatigue. The use of ORR in clinical trials of targeted agents in rare populations has not been formally statistically validated as a surrogate for OS or health related quality of life as phase III trials using OS/health related quality of life endpoints have not been considered feasible or ethical. The CGP felt that an ORR of over 70% as seen in the integrated analysis set is extremely unlikely to not translate to an OS benefit.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Setting	Countries participating in the Trial	No Canadian sites or patients were included in any of the clinical trials included in the integrated analysis. Patients that were recruited in either the integrated safety or efficacy analyses sets came from the following sites: STARTRK-2 trial: United States, Australia, Europe (Belgium, France, Germany, Netherlands, Italy, Poland, Spain, United Kingdom) and Asia (Japan, Republic of Korea, Hong-Kong, Singapore, Republic of Taiwan). Most sites were in the USA. STARTRK-1 trial: United States and the Republic of Korea. Alka trial: Italy.	Are there any known differences in the practice patterns between other participating countries and Canada (that would impact the clinical outcomes, or the resources used to achieve the outcomes)?	The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on different disease management practices across countries.
	Ethnicity or Demographics	Integrated efficacy set (n = 53): White (58.5%), Asian (35.8%), Black/Africa American (5.7%), not reported (0%) Integrated efficacy set (n = 94): White (48.9%), Asian (43.6%), Black/Africa American (5.3%), not reported (2.1%)	Is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?	The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on ethnicity.

1.2.4 Interpretation

There were an estimated 21,000 deaths from lung cancer in 2019 in Canada.[6] Although the majority of lung cancers are tobacco associated, there is an increasing recognition of subsets of patients with cancer originating in the lungs that are not tobacco associated. A subset of these non-tobacco associated cancers is driven by oncogene (cancer) gene activation through genetic translocations. One of these non-smoking associated, oncogene-associated lung cancer is termed ROS-1 translocation positive lung cancer, which affects approximately 200 people per year in Canada, the vast majority being with advanced (stage IV) incurable disease. The actual modifiable or environmental risk factors for ROS-1 positive lung cancer are unknown, and prevention and screening are not likely to impact this disease until those factors can be elucidated. Platinum based doublet chemotherapy has been the backbone of treating metastatic disease for stage IV ROS-1 positive non-small cell lung cancer, but this has changed in recent years. Crizotinib was approved by Health Canada in 2012 for ALK positive NSCLC patients, and in 2017 for ROS-1 positive patients. Crizotinib received a conditional positive final pERC recommendation in 2019 for first-line treatment for patients with ROS-1 positive advanced NSCLC. It is the evolving standard in Canada but not universally funded. For patients for whom crizotinib is available, a ROS-1 translocation may be tested for and the patient offered crizotinib. Following crizotinib, patients typically receive platinum pemetrexed doublet therapy at treatment failure, followed by possibly docetaxel and finally immunotherapy with nivolumab, atezolizumab, or pembrolizumab. In patients for whom crizotinib is not available, ROS-1 is often not tested for, and patients are treated as the general non-small cell lung cancer population with chemotherapy-immunotherapy combination (pembrolizumab, pemetrexed, carboplatin), followed by docetaxel at progression.

Small studies of ROS-1 mutation positive NSCLC patients treated with platinum-based doublet chemotherapy showed that their survival is similar to patients without ROS-1 mutations. Given the rarity of this set of patients, it is unknown if any ROS-1 positive patients were included in the platinum-doublet-immunotherapy clinical trials, but if so it is expected that they were very few in number. For single agent immunotherapy, it is known that therapy is rarely effective in patients with similar demographics to ROS-1 positive patients (i.e., non-smoker, younger), and immunotherapy is saved for 3rd or 4th line therapy. The efficacy of current standard non-oncogene driven systemic therapy (i.e., chemotherapy-immunotherapy) is unclear in this subset, but is unlikely to be more than marginally better than chemotherapy without immunotherapy.

Entrectinib was studied in 3 clinical trials in lung cancer, where a pooled analysis of two phase I studies and one phase II basket trial form the basis of this application, with 53 patients being used for the efficacy set as they had over 12 months of follow-up at the time of analysis (May 31, 2018). Over the course of the review the sponsor provided a larger dataset with n = 94 patients (median follow-up 20.3 months) with analyses reported at the May 1, 2019 data cut-off date. The studies included patients with various fusion oncogenes, including ALK alterations, NTRK fusions and ROS-1 fusions. Safety data included patients with various genetic alternations (e.g., NTRK fusion, ROS-1, ALK fusion), whereas effectiveness data included ROS-1 fusion positive patients only.

Effectiveness: At the May 31, 2018 data cut-off date, objective response rate was 77% with the lower and upper 95% confidence intervals being 64% and 89%, respectively. Responses were similar in those with CNS metastases at baseline and without, and included an intracranial response rate of 55% (11/20), although some of this may have been radiation related. The median duration of response was 25 months, while the median PFS was 19 months. The 18-month survival rate was an impressive 82%.

The updated efficacy results (n = 94) continued to suggest durable responses in a high proportion, including intracranial responses in patients with CNS disease at baseline. However, with regards to comparing the results across the N = 53 and n = 94 populations to assess the consistency of efficacy results, differences in follow-up duration (median 25.4 versus 20.3 months for response follow-up and 25.9 versus 20.9 months for median survival follow-up for the N = 53 and N = 94 populations, respectively) and patient characteristics [the n = 94 data set include less favorable patients, see section 6.3.2.1, c) Populations] should be considered when comparing results between these populations.

At the May 1, 2019 data cut-off date, the objective response rate was 73% with the lower and upper 95% confidence intervals being 63% and 82%, respectively. The intracranial response was 50% (17/ 34). The median duration of response was 16.5 months, while the median PFS was 16.8 months. The 18-month survival rate was 76%.

The report of the combined analysis showed high response rates, durability of response and impressive 18-month survivals rates, better than would be expected in this group had they been treated with platinum doublet chemotherapy with immunotherapy.

Eighteen-month survival rates with platinum-based therapy – immunotherapy combination would be expected to be approximately 55% and response rates of 40-50%, without receiving a ROS-1 inhibitor.

Patient-reported outcomes were collected in the phase II portion of the study only, and numbers were small. At baseline, the Global Health Status/QoL and Functional Scale scores were moderate to high and showed higher values compared to the base line value (higher scores reflecting improvement) at most assessment points, except the cognitive functioning scale that showed worsening scores at most assessment points. For the QLQ-LC13 instrument, patients reported lung symptom burden at baseline with trends toward improvement. Overall, it appears that results cumulated in no specify change in HRQoL. However, patient-reported data must be interpreted with caution as results were summarized descriptively and due to the non-randomized design of the trial, the impact of entrectinib on quality of life in relation to other therapies is unknown.

The lack of a standard comparator arm in the trials limits the interpretation of progression free survival, which in general is a less meaningful endpoint than overall survival or quality of life outcomes. It would be difficult to conduct a randomized trial as the ROS-1 positive patient population is small. A previous CADTH reimbursement review report of crizotinib[7] noted a trial of crizotinib versus chemotherapy may be difficult logistically and ethically, however, an actual clinical trial of active treatment with entrectinib versus crizotinib would not be as challenging ethically or acceptability wise, but would be difficult due to the rarity of the condition. The European Medicine Agency's assessment report states that in order to further characterise the efficacy of entrectinib in patients with baseline CNS disease, results of a randomised controlled trial of entrectinib versus crizotinib in treatment naïve ROS-1 NSCLC patients should be conducted and submitted.[8] The clinicaltrials.gov website lists a phase III trial that will compare the efficacy and safety of entrectinib and crizotinib in participants with advanced or metastatic ROS-1 NSCLC with and without CNS metastases. The estimated study start date is April 30, 2021.[9]

Safety: Entrectinib does not have an insignificant adverse event profile, with 13% of patients having a treatment related serious adverse event, and 7% of patients in the clinical trials having an adverse event leading to death. Thirty-seven percent of patients had a serious adverse event, including a notable percentage (12%) with a serious nervous syndrome or psychiatric disorder. As with all oral anti-cancer agents, education, preparation, monitoring, and attention to these unusual side effects is crucial, particularly when moving from phase I/II into practice. The lack of a large phase III trial, or even a robust phase IV trial makes the actual safety somewhat more uncertain. Despite the clear limitation of this non-comparative efficacy analysis, the CGP agreed that entrectinib appears to have a favourable toxicity profile compared to standard platinum doublet chemotherapy or chemotherapy-immunotherapy combination (pembrolizumab, pemetrexed, carboplatin).

Entrectinib is an oral systemic therapy agent, and in general will be managed with experienced oncology pharmacists and physicians. As with all anticancer oral agents, attention to drug interactions is standard and manageable.

Comparative therapies considered: Currently, only indirect comparisons can be made between entrectinib and crizotinib or platinum doublet chemotherapy. Refer to Section 7 for summaries and critical appraisals of Sponsor-submitted indirect treatment comparisons (ITCs). With regards to the comparison to crizotinib, the CGP noted that results based on a MAIC suggested no statistically significant difference across efficacy outcomes (OS, PFS, ORR) and discontinuation due to AEs between entrectinib and crizotinib. The results based on a propensity score matched comparison analysis suggested a difference in OS, PFS, and time to treatment discontinuation favouring entrectinib over crizotinib. For the comparison of entrectinib versus platinum doublet chemotherapy (pemetrexed/platinum), the results were statistically significantly in favour of entrectinib for OS, PFS, ORR and not statistically significantly different for discontinuation due to AEs. However, the CGP agreed with the CADTH Methods Team, that due to severe limitations identified in the ITCs caution must be used in interpreting the comparative efficacy and safety estimates.

Given the absence of robust comparative evidence it is not possible to ascertain if entrectinib or crizotinib is superior. Therefore, the CGP agreed that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

However, the present results—though from non-comparative trials - compare favourably to currently available therapies, such as platinum doublet chemotherapy with immunotherapy. The results of the integrated efficacy analysis showed high response rates, durability of response and impressive 18-month survivals rates, better than would be expected in this group had they been treated with platinum doublet chemotherapy with immunotherapy.

Burden of Illness: The number of patients requiring treatment would likely be in the order of 200 per year in Canada. As ROS-1 mutation positive lung cancer is more common in younger, non-smoking patients the number of potential years of life lost from this illness would be higher than the average lung cancer patient.

Need: As this is a uniformly fatal disease, there is a need for more effective therapies in this population. Target inhibition with crizotinib has proven effective, but there is not universal access at this time. It is unclear how/if entrectinib would be superior compared with crizotinib, although it possibly may help in cases where patients have CNS metastases at baseline, based on pharmacokinetic/drug distribution. In other oncogene driven cancers such as ALK positive disease, crizotinib is inferior to other agents due to the lack of CNS penetration. As with most conditions, it's beneficial to have more than one option for treatment from both a supply chain perspective (i.e., interruptions in supply from one manufacturer) and from a patient tolerance perspective.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is net clinical benefit to entrectinib compared with standard platinum doublet chemotherapy or chemotherapy-immunotherapy combination (pembrolizumab, pemetrexed, carboplatin), for the first line-treatment of patients with ROS-1 positive locally advanced or metastatic NSCLC. This conclusion is based on a combined analysis of three clinical trials with ROS-1 positive NSCLC patients. The overall response rates were clinically significant, above 70%, clearly exceeding response rates expected with platinum doublet chemotherapy and immunotherapy (~50%). The response rate is similar to that seen in the crizotinib clinical trials, which was also above 70%. The durability of responses, CNS penetration, and robust overall survival results make entrectinib a reasonable treatment option, along with crizotinib, in ROS-1 positive NSCLC. The safety profile of entrectinib was manageable and appears to be better than experienced with chemotherapy with overall no significant detriment to quality of life.

In making this conclusion, the CGP considered:

- The level of evidence in support of this conclusion is limited as there are no randomized trials evaluating entrectinib for ROS-1 positive NSCLC patients. There would be no equipoise if chemotherapy was chosen as a comparator in a randomized comparative trial. Additionally, the small sample size of this patient population given the rarity of ROS-1 mutations may preclude the feasibility of conducting a randomized control trial.
- The CGP notes that the reimbursement request is for entrectinib for first line treatment for patients with ROS-1 positive NSCLC. However, the funding should be for any line of therapy, which aligns with the clinical trial populations, and there is no significant difference in response amongst line of therapy. If entrectinib were to be funded, it should not matter if the patient has already had one or two lines of non-targeted therapy.
- The CGP notes that routine testing for ROS-1 through a validated test will be required in order to facilitate treatment decisions with entrectinib. The CGP recognize that access to ROS-1 testing may be a barrier to implementation because ROS-1 testing is not currently part of standard of care but is becoming a standard with newer next generation sequencing (NGS) panels and other means (IHC followed by FISH).
- Clinical trials and special access programs for targeted therapies, or platinum doublet chemotherapies or docetaxel could be options if disease progression occurs after failure on entrectinib. Patients with driver mutations, including the ROS-1 mutation will likely not be considered for treatment with immunotherapy such as nivolumab or pembrolizumab in the immediate post-progression setting as they are not likely to respond to this type of therapy, and if used in the 3rd or 4th line as 'desperation' therapy, are unlikely to receive more than one or two cycles due to the low expected response rate. However, in the absence of ROS-1 testing or targeted therapy, immunotherapy (pembrolizumab) will be given with chemotherapy (carboplatin/pemetrexed/pembrolizumab) for likely several cycles as initial therapy, as the likelihood of response and a prolonged treatment time will be higher when given with chemotherapy. In other words, in the absence of a targeted therapy option for ROS-1 positive disease, the expected immunotherapy duration of treatment and cost would be significantly higher (as it's given concurrently with chemotherapy in that setting). If a targeted therapy for ROS-1 is available, then if/when immunotherapy is used it would be after failure of multiple lines of therapy, meaning less patients are treated, and as a monotherapy with a low response rate, meaning patients would likely receive a significantly lower numbers of cycles of therapy.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
PAG noted that the standard of care for first-line treatment of patients with ROS-1 mutation positive locally advanced or metastatic NSCLC is crizotinib but this is not universally funded at this time. If first line crizotinib is not available, then chemotherapy (e.g., cisplatin plus pemetrexed) would be an option. • Patients with ≥50% tissue expression of PD-L1 are eligible to receive first-line pembrolizumab, while the latter combined with chemotherapy is reimbursed in most provinces for all patients regardless of PD-L1 expression. However, tumours must not harbor a sensitizing EGFR mutation or ALK translocation. PAG would like confirmation that the same would apply for ROS-1 rearrangement in practice and that first-line pembrolizumab should not be used in this population.	The CGP noted that approximately one third of ROS-1 positive patients will present with 50% or greater tissue expression of PD-L1. The CGP agreed that for patients with ROS-1 positive status crizotinib would currently be the preferred first-line option. However, while in current clinical practice PD-L1 status is usually known ROS-1 status may not be known. If the ROS-1 status of patients is not known in patients with 50% or greater PD-L1 expression, then pembrolizumab in combination with chemotherapy or pembrolizumab alone may be offered. Many of these patients would have clinical features that may suggest choosing pembrolizumab in combination with chemotherapy over pembrolizumab alone. If patients with 50% or greater PD-L1 tissue expression are known to have ROS-1 positive status but crizotinib is not available, then either pembrolizumab in combination with chemotherapy or pembrolizumab alone would be reasonable options. The CGP noted that it is generally accepted that pembrolizumab may be less effective as a monotherapy in the present target population, but the number of ROS-1 positive patients enrolled in pivotal clinical immunotherapy trials is extremely small.
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with entrectinib: • Patients with poor performance status (i.e., ECOG PS of 2 or greater).	• The integrated data set (pooled analysis across the ALKA-372-001, STARTRK-1 and STARTRK-2 trials) was limited to patients with ECOG PS of 2 or less. Most patients had ECOG PS of 1. The CGP supports generalization of the entrectinib treatment effect to patients with ECOG PS of 2 or greater. In general, oncogene targeted therapies have a rapid onset of action and toxicity is manageable in an ECOG 2/3 group, just as osimertinib (in EGFR positive patients) or alectinib (in ALK positive) are used in these populations. A very small proportion of patients in clinical practice have ECOG PS of greater than 2. The CGP noted that clinicians generally offer targeted therapies to patients with ECOG PS of 2 or greater. The ECOG PS may be related to the underlying disease/ tumour symptoms and would be expected to improve on treatment.
If recommended for reimbursement, PAG noted that the following groups of patients would need to be addressed on a time-limited basis: • Patients with ROS-1 positive NSCLC who are currently receiving either first-line chemotherapy, PD-1 inhibitors, or crizotinib	The CGP noted that it would be reasonable to offer entrectinib on a time-limited basis to patients who have initiated first-line platinum-based doublet chemotherapy, chemotherapy-immunotherapy combination, or single agent immunotherapy (pembrolizumab monotherapy) and have not progressed, and to fund patients at any line of therapy if not having received a ROS-1 targeted treatment previously. However, the CGP noted that there is insufficient evidence to ascertain the treatment effect of entrectinib in patients who have started treatment with crizotinib and have not progressed.

PAG Implementation Questions	CGP Response
	Furthermore, the CGP noted that there is currently no robust comparative evidence to ascertain which of the agents (i.e., entrectinib or crizotinib) has superior efficacy. For these reasons the CGP does not support offering entrectinib on a time-limited basis in patients who are currently on crizotinib and have not progressed, unless the patient is experiencing intolerable toxicity from crizotinib.
• Since entrectinib was approved by Health Canada for ROS-1 positive advanced or metastatic NSCLC not previously treated with crizotinib, PAG noted that there may be pressure to reimburse the drug for this indication beyond first line, should the recommendation align with the sponsor-requested criteria • Patients with NTRK+ or ALK+ tumours as well as treatment in the adjuvant setting (in the event there is reflex ROS-1 testing) would be considered out of scope of the current review.	• The eligibility criteria of the integrated data set (pooled analysis across the ALKA-372-001, STARTRK-1 and STARTRK-2 trials), did not restrict the number of previous lines of systemic therapy. The majority of patients (86.8%) had at least one prior therapy for advance or metastatic disease. The most commonly received anti-cancer therapy was chemotherapy. The CGP noted that the benefit of treatment with entrectinib was seen for all patients with ROS-1 positive advanced or metastatic NSCLC regardless of line of therapy. However, the CGP agreed that patients should not have previously been treated with a ROS-1 targeted therapy, such as crizotinib. • As patients with NTRK+ or ALK+ tumours were excluded from the integrated data set (pooled analysis across the ALKA-372-001, STARTRK-1 and STARTRK-2 trials), there is insufficient data to support the generalizability of treatment benefit with entrectinib to patients with other mutations than ROS-1. The CGP also did not support generalizing the treatment effect of entrectinib to the adjuvant setting, as entrectinib has not been studied in this setting.
Implementation Factors	
Entrectinib is administered once daily which is an enabler to implementation. PAG noted the recommended dose is 3 capsules daily which may represent pill burden.	The CGP noted that they do not expect the pill burden to be a significant barrier to implementation. Most patients in the integrated efficacy analysis were below the age of 65 years, which is representative of patients seen in clinical practice. The CGP did not anticipate significant swallowing difficulties or challenges with taking 3 capsules daily in these patients.
Additional health care resources (e.g., frequent clinic visits while patients are on therapy) are required for monitoring adverse effects and tolerability with entrectinib. Increased pharmacy time would be required for dispensing entrectinib.	Compared to crizotinib the CGP did not anticipate that entrectinib would require increased frequency of clinical visits for monitoring of blood work and side effects.
Sequencing and Priority of Treatment	
PAG is seeking to confirm place in therapy with entrectinib and optimal sequencing with chemotherapy, crizotinib, and PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab) for ROS-1 NSCLC: • Is entrectinib the preferred first-line agent for ROS-1 mutations? PAG is seeking clarity on whether crizotinib and entrectinib are therapeutically equivalent for the treatment of ROS-1 mutated NSCLC.	• Currently, only indirect comparisons can be made between entrectinib and crizotinib. Refer to Section 7 for summaries and critical appraisals of Sponsor-submitted indirect treatment comparisons (ITCs). The CGP noted that results based on the MAIC suggested no statistically significant difference across efficacy outcomes (OS, PFS, ORR) and discontinuation due to AEs between entrectinib and crizotinib. The results based on a propensity score matched comparison analysis suggested a difference in OS, PFS, and time to treatment discontinuation favouring entrectinib over crizotinib. However, the CGP agreed with the CADTH Methods Team, that due to severe limitations identified in the ITCs caution must be used in interpreting the

PAG Implementation Questions	CGP Response
	comparative efficacy and safety estimates. Given the absence of robust comparative evidence it is not possible to ascertain which of the agents (i.e., entrectinib or crizotinib) is superior. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
• In what clinical scenarios (e.g., CNS involvement) would entrectinib or crizotinib be the preferred treatment for ROS-1 NSCLC?	• While there is insufficient evidence regarding CNS activity of crizotinib, limited evidence suggests that entrectinib has some CNS activity. In the integrated efficacy analyses, intracranial objective response rate by BICR was seen in approximately half of the patients with CNS metastases at baseline. The CGP anticipated that most clinicians would prefer to use entrectinib over crizotinib in patients with CNS metastases. The lack of sufficient efficacy of crizotinib in other CNS predominant lung subtypes (i.e., ALK positive) is likely transferrable to this ROS-1 setting.
• Can entrectinib be used when a ROS-1 positive tumour acquires a mutation conferring resistance to crizotinib, or vice versa?	• The CGP noted that there is currently insufficient evidence to guide a recommendation on whether entrectinib can be used when a ROS-1 positive tumour acquires a mutation conferring resistance to crizotinib.
• Is there evidence to inform use of entrectinib in patients with ROS-1 positive NSCLC who experience CNS disease progression on first-line crizotinib?	• In the absence of sufficient evidence to guide this decision, the CGP noted that there is a pharmacokinetic advantage for entrectinib in terms of CNS penetration. Therefore, there is a clinical rationale to offer entrectinib after crizotinib if the only site of progression is intracranial. The STARTRK-2 trial allowed entry of patients with ALK or ROS-1 rearranged NSCLC with CNS-only progression who were previously treated with crizotinib.
• PAG is seeking confirmation that patients who started chemotherapy, or PD-1 inhibitors while waiting for ROS-1 test results be switched to entrectinib should the results be positive.	• The CGP agreed that targeted therapy is regarded as superior to chemotherapy, single agent immunotherapy, or chemotherapy-immunotherapy combination in this setting. The CGP supports that patients who started chemotherapy, single agent immunotherapy, or chemotherapy-immunotherapy combination while waiting for ROS-1 test results, should be switched to entrectinib should the results be positive.
• PAG is also seeking confirmation that patients cannot have both ROS-1 and NTRK mutations.	• Driver mutations (ROS-1, NTRK, EGFR, and ALK) are mutually exclusive. That is, the ROS-1 mutation is exclusive of other oncogenic drivers and is considered nonoverlapping. It is extremely rare that patients will present with more than one mutation at the same time.
• Is there any evidence to support the use of PD-1 or PD-L1 inhibitors after entrectinib?	• The CGP noted patients with driver mutations, including the ROS-1 mutation will likely not be considered for treatment with immunotherapy such as nivolumab or pembrolizumab in the immediate post-progression setting as it is know that single agent immunotherapy is rarely effective in patients with similar demographics to ROS-1 positive patients (i.e. non-smoker, younger).

PAG Implementation Questions	CGP Response
	In the absence of sufficient evidence to guide this decision, possible treatment options upon progression on entrectinib or crizotinib include clinical trials, special access programs for targeted therapies, or chemotherapy (carboplatin/pemetrexed), followed by either docetaxel or single agent immunotherapy.
Would entrectinib be used after crizotinib or other ROS-1 targeted agents but before subsequent therapies? Or would entrectinib be used more in later lines or last resort therapy?	The CGP noted that if both entrectinib and crizotinib were funded, it would be reasonable to switch from one treatment to another if there is intolerance or intolerable side effects. The CGP noted, however, that it is currently unclear what the degree of cross-resistance is between crizotinib and entrectinib. There is a pharmacokinetic advantage for entrectinib in terms of CNS penetration, so there is a clinical rationale to try entrectinib after crizotinib if the only site of progression is intracranial. However, outside of these specific situations, there is no role for switching from one ROS-1 inhibitor to another. There is currently insufficient evidence to guide treatment with entrectinib in later lines of therapy or as last resort therapy in patients who have received first-line crizotinib.
Companion Diagnostic Testing	
PAG noted that ROS-1 is not routinely available in all provinces. PAG members noted there is no formalized testing process or funding in place for ROS-1 in jurisdictions. Health care resources and coordination to conduct the ROS-1 testing in the first-line setting will be required. The significant increase in costs for ROS-1 testing is a barrier to implementation.	
PAG had concerns related to: • the turnaround time for ROS-1 testing	• The CGP noted that overall NGS multiplex testing is becoming more common, with turn around times of one or a few weeks. Turn around times are similar between tests for targeted therapies (e.g., EGFR).
• whether all NSCLC patients are required to be tested for ROS-1	• For patient with nonsquamous NSCLC, the CGP noted that it would be desirable for jurisdictions to have validated and reliable ROS-1 testing available to identify the relevant patient population.
• how testing is performed (i.e., through IHC or FISH or other methods)	• The CGP noted that ROS-1 testing using a validated test authorized by Health Canada or one that is equivalent to that used in the ALKA-372-001, STARTRK-1 and STARTRK-2 trials, would be reasonable, such as IHC followed by confirmation test with FISH or NGS.
• as patients are currently tested for EGFR, PD-L1, and ALK in the first-line setting, whether there will be enough tissue sample to test for ROS-1 as the fourth test.	• CGP noted that if testing is done sequentially with single-gene assays, availability of tissue may become a problem. However, NGS testing avoids this problem by allowing parallel sequencing with small tumor samples.

ALK = anaplastic lymphoma kinase, BICR = Blinded Independent Central Review, CGP = Clinical Guidance Panel, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = Epidermal growth factor receptor; FISH = Fluorescence in situ hybridization, IHC = ImmunoHistoChemistry, MAIC = matched adjusted indirect comparison, NGS = next generation sequencing, NSCLC = non small cell lung cancer; NTRK = neurotrophic receptor tyrosine kinase, PAG = Provincial Advisory Group; ORR = objective response rate,
OS = overall survival, PD-L1 = Programmed death-ligand 1; PFS = progression-free survival.

2 Background Clinical Information

2.1 Description of the Condition

Lung cancer is the second-most diagnosed cancer in both men and women and is the leading cause of cancer deaths in Canada. It is estimated that in 2019, there were 29,300 new cases of lung cancer diagnosed and 21,000 deaths associated with lung cancer, with 48.1/100,000 deaths.[6] NSCLC represents approximately 85 % of all cases of lung cancer and for the purposes of therapeutic decision, are categorized by histologic appearance as either squamous or non-squamous NSCLC. The majority of patients with NSCLC will present with or develop advanced/ metastatic disease. For these patients, treatment intent is to palliate symptoms and prolong survival. In patients with non-squamous NSCLC, the first step in determining treatment options is assessment of molecular markers, including chromosomal rearrangement of the Anaplastic Lymphoma Kinase (ALK) gene on chromosome 2 (ALK positive NSCLC), and most recently ROS-fusion positive. The prognosis of patients with advanced NSCLC is poor, with a median survival of 8–10 months and a 2-year survival of approximately 10%.[10] The 5-year survival for patients with clinical stage IV disease has been estimated at less than 5%.[11]

ROS fusion positive non-small cell lung cancer is a lung cancer for which no modifiable risk factors are known. It is not caused by cigarette or tobacco exposure, and patients tend to be younger and have less tobacco exposure than lung cancer without EGFR/ALK/ROS fusions. For advanced lung cancer, the incidence of ROS-1 positive cancers varies, but is thought to be between approximately 1% - 2% of patients with NSCLC.[8]

The Canadian Cancer Society estimates that in 2019, there are approximately 29,300 new cases of lung cancer in Canada.[6] Estimating that 85 % are NSCLC, 70 % of which present with advanced / metastatic disease, and 1 % of those are ROS-1 -positive, the estimate of the number of advanced ROS-1 NSCLC cases in Canada in 2019 is approximately 200. A true determination of this number is not clear as testing for ROS-1 is not universally available. Testing may include next generation sequencing, or an IHC screen followed by fluorescent in-situ hybridization.

While ROS-1 patients were not excluded from clinical trials for non-driver mutation non-small cell lung cancer, the rarity of this subtype would mean only a very small number (if any) patients would have been included in the early chemotherapy trials, or in immunotherapy trials.

The 2017 ASCO guidelines[12] recommended crizotinib in the first-or second-line setting. Since that time, further phase II data were published with crizotinib, including the cohort in the 2017 guidelines described by Goto et al.[13] and subsequently published by Wu et al[14], and a separate European cohort of 34 patients published by Michels et al.[15] Results for crizotinib have consistently shown a response rate of over 70%, a median PFS greater than 12 months and one-year OS rate of more than 80% in separate phase II trials. Similar high response rates were found with entrectinib on an ongoing pooled analysis of three studies (ALKA, STARTRK-1, and STARTRK-2) (77%), with a median PFS of 19 months. Ceritinib had a response rate of 63%[16], and all patients were pretreated with chemotherapy, while lorlatinib had a response rate of 62% in non-crizotinib pre-treated patients.[17] Although comparing phase II data regarding toxicity is a challenge, there are sufficient toxicity data to reasonably conclude that lorlatinib has more side effects.

In patients whose disease progresses on targeted therapy – typically crizotinib – there is a paucity of data, as only two patients in the ceritinib study[16] received prior crizotinib. The lorlatinib study[17] included 40 patients pretreated with crizotinib, with a RR of 35%, and a median PFS of 8.5 months. These data were insufficient to recommend a therapy in this setting and did not clearly show better efficacy than chemotherapy or chemotherapy/immunotherapy.

2.2 Accepted Clinical Practice

Currently in Canada, clinical practice depends on if ROS-1 testing is done, as ROS-1 testing is only helpful if a clinical decision is needed. In the metastatic setting, in areas where ROS-1 is unknown, or targeted therapy is unavailable, standard treatment is chemotherapy-immunotherapy combination (pembrolizumab, pemetrexed, carboplatin), based on the Keynote 189 clinical trial.[18] This treatment combines chemotherapy with immunotherapy and is associated in general with a high response rate (approximately

50%%), and a median overall survival for all comers of 22 months.[19] As ROS-1 was not tested for in this trial, it's impossible to know what the actual number of patients in the trial or the actual benefit for this small subgroup of patients is.

Platinum-based doublets have been the backbone of first-line treatment of patients with advanced NSCLC with a median OS that does not exceed one year.[20] Small studies of ROS-1 mutation positive NSCLC patients treated with platinum-based doublet chemotherapy shows that their survival is similar to patients without ROS-1 mutations. Given the rarity of this set of patients, it is unknown if any ROS-1 positive patients were included in the platinum-doublet-immunotherapy clinical trials, but if so it is expected that they were very rare. For single agent immunotherapy, it is known that therapy is rarely effective in patients with similar demographics to ROS-1 positive patients (i.e., non-smoker, younger), and immunotherapy is saved for 3rd or 4th line therapy. The efficacy of current standard non-oncogene driven systemic therapy (i.e., chemotherapy-immunotherapy) is unclear in this subset, but is unlikely to be more than marginally better than chemotherapy without immunotherapy.

In areas where ROS-1 testing and crizotinib are available, crizotinib is the standard first choice for first line therapy. Crizotinib is an oral small molecule inhibitor of ALK, MET and ROS-1 kinase. Until recently, crizotinib was the accepted first-line therapy for metastatic ALK positive NSCLC in Canada and publicly funded for this indication; it was also recently approved by CADTH for the use in ROS-1 positive patients. Crizotinib was recommended in ASCO guidelines in 2017 based on phase II data with response rates of greater than 70% in multiple phase II trials, and one year overall survivals rates of over 80%.[12] Crizotinib is the standard first line choice for ROS-1 NSCLC where available, and second- or third-line choice if not received previously. Entrectinib is yet another oral ROS targeted tyrosine kinase inhibitor, with good CNS penetration, and also active in NTRK fusion positive patients. It was tested in multiple single-arm phase 1 trials, and a pooled analysis of three studies; results showed a response rate of 77%, with a median PFS of 19 months.

In terms of consideration for reimbursement, there will be several groups of patients with different treatment pathways who need to be considered; these patients will likely be eligible for entrectinib at different times. For patients diagnosed with lung cancer who are currently on therapy, the majority will be treated with chemotherapy and immunotherapy combination or sequentially. For these patients, if found to be ROS-1 positive, entrectinib would need to be available in second or third line. Other patients will be newly diagnosed, and if tested before any treatment initiation, would be treated with entrectinib.

For funding considerations, the cost of not testing for ROS-1 and treating with targeted therapy would be the cost of chemotherapy and immunotherapy combination therapy. If ROS-1 testing revealed a ROS-1 positive cancer, the treatment algorithm would be entrectinib or crizotinib followed by chemotherapy at progression (carboplatin/pemetrexed), followed by either docetaxel or single agent immunotherapy.

From a reimbursement perspective, CADTH currently does not have a separate process for rare disease. ROS-1 positive lung cancer should be seen as a rare disease, rather than as a rare subset of a common disease. There are significant practical challenges of conducting a robust phase III in such a rare disease and there is a significant unmet medical need for these unfortunate patients with a rare tumour.

3 Summary of Patient Advocacy Group Input

LCC provided input on entrectinib (Rozlytrek) as a monotherapy for the first-line treatment of patients with ROS-1 positive locally advanced or metastatic NSCLC. The input was gathered from the 1) Faces of Lung Cancer Survey and 2) an environmental scan of online forums, individual interviews, and survey responses of ROS-1 positive NSCLC patients. The Faces of Lung Cancer Survey was conducted nationally in August 2015. There were 91 patient and 72 caregiver respondents; at the time of the survey, all patients were living with lung cancer or had lung cancer and all caregivers were currently caring or previously cared for patients living with lung cancer. However, according to LCC none of the patients from this survey met the funding request under review—for the first-line treatment of adult patients with ROS-1 positive locally advanced or metastatic NSCLC. The environmental scan was performed between December 2019 and January 2020. Among the data collected, 15 patients and one caregiver provided input; however, none were Canadian. Information was gathered from the US (n = 11), Belgium (n = 1), Austria (n = 1), Spain (n = 1), UK (n = 1), and Australia (n = 1—caregiver). Additionally, all patients and caregivers had experience with entrectinib but not necessarily in the first-line setting. The environmental scan demonstrated that the ROS-1 mutation is more common in females, the younger population, and non-smokers, which was noted to be observed and well documented. A summary of the information gathered is found in Table 4.

LCC highlighted that ROS-1 positive NSCLC patients have limited options. Crizotinib is the agreed upon standard of care; however, it is not funded in Canada and is not affordable. Alternative options include chemotherapy, which is associated with significant side effects and multiple, long hospital trips for administration. Additionally, time taken off of work to address the needs associated with chemotherapy is particularly substantial for this population as patients tend to be younger; thus, handling financial hardships, competing family priorities, and care related to the disease and treatment results in a significant physical and psychological burden for the patient and caregiver. Immunotherapy is another option, which has more manageable side effects but has been shown to work poorly in ROS-1 positive NSCLC patients regardless of PD-L1 status. LCC stated that Canadians have a higher disease burden compared to the rest of the world due to the limited access to oral therapies that are more effective than chemotherapy and allow for a higher quality of life.

Regarding treatment expectations, patients value treatment efficacy; treatment convenience; more manageable side effects; and treatment outcomes such as improved symptoms, quality of life, and survival rates or maintaining a progression-free state. Entrectinib being an oral medication would improve treatment convenience as this method of delivery lessens a significant amount of stress and dependency on caregivers by reducing the need for multiple, long hospital visits for intravenous administration. Patients also hope to access entrectinib as it could address the unmet need of treating CNS metastases since entrectinib has been demonstrated to have better blood-brain barrier penetration compared to crizotinib.

Among those with treatment experience, entrectinib was summarized to control the cancer; elicit manageable side effects; improve treatment experience due to the feasible administration; and allow patients to enjoy life activities, remain independent, live a new normal, and for some patients to return to work. Namely, among the 16 responses gathered by the LCC, seven patients had a duration of response of more than 19 months and two patients had no evidence of disease. The side effects associated with entrectinib were reported by most patients to be manageable. Edema/ weight gain, followed by taste changes and fatigue were the most commonly reported side effects. The oral administration of entrectinib improved treatment experience as patients were able to take their medication at home and there was a reduced need for injections and long hospital visits or stays. Patients reported feeling less tired after treatment and could attend appointments on their own, which alleviated the burden on caregivers. Moreover, entrectinib allowed some patients to achieve a high level of functionality to return to work, which is important for NSCLC patients who are typically younger. Overall, entrectinib has allowed patients to enjoy life activities, stay active, try new activities, remain independent, and live a new normal.

Ultimately, LCC specified that the goal of cancer treatment is to provide the right drug for the right target and person. Notably, entrectinib not only personalizes the treatment but also addresses CNS presentations and allows patients to live well, achieve new life milestones, and spend more time with family and loved ones. There are a number of approved targeted forms of treatment for other molecular driven cancers such as EGFR and ALK NSCLC; thus, patients with the ROS-1 mutation should also be given the same opportunities. Additionally, with the likelihood of CNS involvement at diagnosis or post-treatment, which is a frequent cause of morbidity and mortality, entrectinib is a viable option that addresses this need. First-line crizotinib is currently still in pricing negotiations and studies have shown that it may not penetrate the blood brain barrier. The LCC also mentioned the unlikelihood of a

phase III trial being conducted soon; accordingly, they ask that a conditional approval be granted as this would allow the collection of third-line data while providing access to patients and to allow for the collection of real-world evidence.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

Table 4: Summary of Information Gathered by LCC

Patient Group	Information Gathering Method and Number of Respondents
LCC	1. **Faces of Lung Cancer Survey** — National Survey (August 2015) • 91 patient respondents — none met the funding request under review***** • 72 caregiver respondents 2. **Environmental Scan:** online forums, individual interviews, and survey responses (December 2019-January 2020) • 15 patient respondents • 1 caregiver respondent • No Canadian respondents • Note: all respondents had experience with entrectinib but not necessarily in the first-line setting

*****funding request under review: for the first-line treatment of adult patients with ROS-1 positive locally advanced or metastatic NSCLC

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

LCC reported that patients felt scared about their health, overwhelmed about treatment options and survival, and worried about their loved ones and the future when diagnosed with lung cancer. Moreover, advanced ROS-1 positive NSCLC was noted to be commonly associated with CNS metastases. LCC highlighted that ROS-1 positive NSCLC patients around the globe have been treated with oral therapy for years; thus, Canada is falling behind. As a result, the disease experience for patients outside of Canada is very different from the Canadian experience. Oral treatments improve quality of life as opposed to other therapies such as chemotherapy, which is not as effective and elicits a poorer quality of life. Overall, LCC stated that Canadians have a higher disease burden compared to the rest of the world.

3.1.2 Patients' Experiences with Current Therapy

LCC noted that current first-line standard of care for ROS-1 positive NSCLC includes crizotinib and chemotherapy. Immunotherapy may be used for treatment of targeted mutations but this practice is more standard in treatment of PD-L1 positive tumours. Overall, ROS-1 positive NSCLC patients have limited options. Crizotinib is the agreed upon standard of care; however, it is not funded by the provinces and is not affordable. This leaves patients with chemotherapy, which is associated with significant side effects, and immunotherapy, which has more manageable side effects but has been shown to work poorly in these patients regardless of their PD-L1 status. Additionally, many patients present with CNS spread at diagnosis, and the LCC reported that an estimated 25 to 40% of patients develop brain metastases within the first two years of treatment. Studies have shown that while crizotinib and chemotherapy work to treat the cancer and shrink tumors; crizotinib does not appear to penetrate the blood-brain barrier well. Of note, LCC stated to refer to previously submitted inputs for more detailed descriptions of crizotinib and immunotherapies; however, a summary of current therapies follow in the next paragraph.

1. Crizotinib (Xalkori) for ROS-1 positive advanced NSCLC (pCODR 10151)

Immunotherapies:

2. Pembrolizumab (Keytruda) for NSCLC (first-line) (pCODR 10101)
3. Nivolumab (Opdivo) for NSCLC (pCODR 10069)

LCC stated that patients reported a tremendous response with crizotinib, which far exceeded the trial results and expectations of survivorship for a lung cancer population. Patients treated with crizotinib commented that they felt substantially better with crizotinib compared to chemotherapy. Patients reported a better quality of life and greater reductions in disease symptoms such as shortness of breath, chest pain, and fatigue. Side effects were quite manageable and many were able to complete their day to day activities and live a normal life. Patients highlighted the ease of crizotinib administration compared to the stress associated with chemotherapy. The oral administration of crizotinib (twice daily), allowed for patients to take crizotinib at home, which reduced the need for injections and long hospital visits or stays. Accordingly, patients felt less tired after treatment and were able to go to appointments on their own, which alleviated the burden on patients and caregivers. Overall, ROS-1 positive NSCLC patients treated with crizotinib were able to go back to work, enjoy life activities, and remain independent, which allowed patients to achieve a highly functional state that was close to their normal.

LCC noted that chemotherapy works to shrink and inhibit further growth of the tumour but not well. Patients reported experiencing side effects that interfered with daily activities such as nausea, vomiting, and extreme fatigue. Additionally, patients had to cope with toxicities, after-effects, and the inconvenience of multiple hospital visits for the intravenous infusions. Accordingly, patients needed to recover after each infusion, which took away time that could have been spent at work or with loved ones. Namely, the patients' inability to work and the caregivers need to take time off work (to accompany and care for the patient) can lead to a financial hardship for some families. Overall, the "cycle" of chemotherapy extends beyond the hospital visit and results in a physical and psychological burden. In one patient's words, "*I spend half my time between infusions recovering from the side effects, a short time being able to function and then the rest of the time dreading the start of the cycle*."

LCC reported that immunotherapy is generally associated with less side effects compared to chemotherapy and has allowed patients to hope for improved outcomes and live a high quality for life; however, it does not work well in this group of patients. Patients with targeted mutations do not typically do well on immunotherapy and it is not recognized as standard of care. Overall, the LCC reported conflicting experiences with immunotherapy. Some patients reported none to mild side effects that were easily managed; alternatively, some had stronger side effects that were managed by over the counter or prescription drugs. Many found that immunotherapy was tolerable and did not interfere with daily life; for these patients, immunotherapy allowed patients to get out of bed and find a "*new normal*". On the other hand, some patients developed immune-related side effects such as pneumonitis and abnormal thyroid hormone levels (more severe cases), which were treated with prednisolone and thyroid supplements, respectively. Similar to chemotherapy, immunotherapy is administered intravenously, which results in interruptions to daily schedules due to potentially long stays at the hospital and the need for a caregiver to accompany a patient. The burden is particularly impactful due to the relatively younger population of ROS-1 positive NSCLC patients; thus, both treatments may substantially interfere with the ability to work resulting in financial hardships and the ability to handle other family-related priorities.

3.1.3 Impact on Caregivers

LCC highlighted that a diagnosis of lung cancer affects the caregivers in addition to patients. Due to the low survival rate, many caregivers worry about the ultimate outcome, possibility of survival, and how they would cope in the event of death of a loved one. Caregivers may also experience stigma because of the negative implications associated with lung cancer. Thus, caregivers may experience anxiety and depression and may isolate themselves due to the emotional burden. Additionally, caregivers must coordinate care or independently take on various activities to help patients cope with the disease symptoms, treatment administration, and treatment side effects. The emotional toll caregivers experience may ultimately affect the care they provide; therefore, resulting in a lower quality of life for both the caregiver and patient.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Expectations for entrectinib were summarized to include efficacy, convenience, and more manageable side effects compared to current therapies. Patients reported wanting a treatment option that would improve symptoms, quality of life, and survival rates or maintaining a progression-free state. Entrectinib being an oral medication improves the convenience of administration as this method of delivery decreases a significant amount of stress and dependency on caregivers by reducing the need for multiple, long hospital visits for intravenous administration. Targeted therapies have been shown to allow patients to continue working and to live "normal"

and active lives. As mentioned above, this is particularly relevant for this patient population since the ROS-1 mutation is typically found in the younger population. Additionally, entrectinib could address the unmet need of treating CNS metastases, which are common at diagnosis and post-treatment. Entrectinib appears to have better brain penetration than crizotinib and elicited a reduction in the size of brain metastases in 55% of patients who were administered entrectinib in a clinical trial. Overall, entrectinib is expected to treat the tumour with less side effects, which allows patients to have a good quality of live and longer survival.

3.2.2 Patient Experiences to Date

LCC gathered data from 15 patients and one caregiver through interviews, questionnaires, and an online forum on the experience with entrectinib for the treatment of ROS-1 positive NSCLC. As entrectinib is currently not available or funded in Canada, none of the respondents were from Canada; accordingly, respondents were from the US (n = 11), Belgium (n = 1), Austria (n = 1), Spain (n = 1), UK (n = 1), and Australia (n = 1—caregiver). Input provided represented a sample of patients with an average age of 51 (range: 27 to 67) and there were 13 female and three male patients. At the time of the survey, 13 patients were still on entrectinib and three patients were no longer on entrectinib; namely, nine patients received or were receiving entrectinib in the first-line setting, two patients who are no longer on entrectinib received it in the second-line setting, one patient indicated that they are receiving entrectinib in the third-line setting, and four patients indicated they did not receive entrectinib in the first-line setting but did not specify the treatment line. The most commonly noted response elicited by entrectinib was a reduction in tumour size followed by a stable condition. One patient specified that their CNS disease was stable but experienced lung progression and another patient specified that there was no evidence of disease (NED) after eight months. Namely, the latter patient experienced the longest duration of response of four years (diagnosed in 2015). Alternatively, two patients noted that it was too soon to tell their response; one was diagnosed in 2019 and the other in 2018. A summary of the 16 responses and the demographics are exhibited in Table 5.

Table 5: Summary of Demographics and Experiences of Patients and Caregivers with Entrectinib for Treatment of ROS-1 positive NSCLC, LCC

Age	Gender	Date of Diagnosis	Responses	Duration of Responses	Patient/Caregiver	Still on Entrectinib	1st Line Treatment	Location	Source
67	Female	2017	Reduction in the size of the tumors and is currently stable	31 months	Patient	Yes	Yes	USA	Interview
59	Female	2015	Reduction in the size of the tumor	2 years	Patient	Yes	No, first had chemotherapy	Belgium	Questionnaire
56	Female	2014	Stable	3 years	Patient	Yes	3rd line	USA	Questionnaire
43	Female	2013	Stable	11 months	Patient	No	2nd line	USA	Questionnaire
61	Female	2019	Too soon to tell		Patient	Yes	Yes	USA	Questionnaire
41	Female	2018	Too soon to tell	6 weeks	Patient	Yes	No, first had chemotherapy	USA	Questionnaire
41	Female	2019	Reduced tumor size	6 weeks	Patient	Yes	Yes	Austria	Questionnaire
46	Male	2019	60% reduction in tumor size	4 months	Patient	Yes	Yes	Spain	Questionnaire
50	Female	2015	NED after 8 months	4 years	Patient	Yes	No	USA	Questionnaire
52	Female	2017	Reduction in CNS and lung tumors. Currently stable	30 months	Patient	Yes	Yes	USA	Questionnaire
54	Male	2018	NED	2 years	Patient	Yes	Yes	USA	Questionnaire
61	Female	2016	Stable	2 years	Patient	Yes	Yes	United Kingdom	Questionnaire
48	Female	2016	Reduction in tumor size	6 months	Caregiver	No	No	Australia	Questionnaire
60	Female	2016	Stable CNS but lung progression	18 months	Patient	No	No, 2nd line	USA	Questionnaire
54	Male	2018	66% reduction in tumours	15 months	Patient	Yes	1st	USA	Interview
27	Female	2017	Tumor shrinkage	2 years	Patient	Yes	Yes	USa	Online Forum

Overall, entrectinib was summarized by LCC to 1) control the cancer; 2) elicit manageable side effects; 3) improve treatment experience due to feasible administration; 4) allow patients to enjoy life activities, remain independent, and live a new normal; and 5) allow some patients to return to work.

Among the 16 responses exhibited in Table 5, entrectinib was summarized to control the cancer. Namely, seven patients had a duration of response of more than 19 months and two had no evidence of disease; thus, the patient-reported outcomes demonstrate good responses. Additionally, this is demonstrated in the experiences of three patients described by LCC.

- JE has been on entrectinib for two years in the first-line setting and is currently NED. JE is one of the two patients who is NED. "*I am unable to fully describe how I feel, but I am thankful I am still here with my wife and children*."
- LE's spouse was treated with entrectinib for approximately six months. There was a reduction in tumour size and in LE's words, "*He was basically brought back to life. When it was effective, he had quality of life like a normal person*."
- ME began entrectinib following CNS progression on crizotinib. Entrectinib stabilized the disease throughout her body and brain for 18 months upon which she then progressed in the lungs.

Additionally, the side effects associated with entrectinib were reported by most patients to be manageable. Edema/ weight gain (n = 6), followed by taste changes (n = 5) and fatigue (n = 5) were the commonly reported side effects (Table 6). Specific patient experiences with side effects are summarized below.

- For RP, side effects were managed with dose reduction. RP's dose was reduced from 600 mg to 400 mg due to hallucinations experienced at the higher dose. RP is grateful for the drug and to be alive; her optimism is reflected in her own words "*As long as I wake up every day, it is a fantastic day."* She says entrectinib is life saving and she has an excellent quality of life. She tries to do as much as she can and treats her condition as a chronic disease.
- ME developed constipation, taste changes, balance issues, and dizziness occasionally. Despite entrectinib affecting her ability to have an active lifestyle (like she did before she got sick), she still has a reasonable quality of life—it is just different. She is grateful to have a treatment that has allowed her to live.
- AE has been on the entrectinib for two years and has had no side effects and is independent, functional, and physically active at the same level as before her diagnosis.
- DE was initially too sick to work when she was diagnosed and complained of fatigue, light headedness, and taste changes; however, she is now back to work 25 hours per week.
- BE is self-employed and can still work. She complained of dizziness, edema, and weight gain. She is mostly independent and can take of herself and has a very good quality of life.
- KE developed taste changes, weight gain, and swollen feet while on entrectinib. She is still able to work; although, she works from home. She has experienced challenges from entrectinib and sometimes has to rely on her spouse to take her out. Although she feels that she has lost some of her independence and her quality of life is not what it was prior to her diagnosis, she says, "*My life is still worth living.*"

Table 6: Reported Side Effects with Entrectinib, modified from LCC (n = 16)

Side Effects	Number of Patients	Side Effects	Number of Patients
Static Hypotension	2	Constipation	3
Diarrhea	1	Taste Changes	5
Edema/weight gain	6	Fatigue	5
Dizziness	3	Brain fog	3
Nausea	1	Light headedness	1
Joint pain	2	Neuralgia/neuropathy	4
Muscle pain	1	Balance issues	2
Skin pain	2	Increased appetite	1
Increased creatinine	1		

3.3 Companion Diagnostic Testing

LCC noted that detection of ROS-1 requires a tissue based test, which may pose barriers for some patients (e.g., inadequate tissue sample for testing and time required for testing). Thus, the LCC stated that there is a need for more efficient and less invasive testing procedures as the companion diagnostic test should not be a barrier to treatment. LCC indicated that next generation panel testing and blood based tests must be explored in order to truly provide personalized medicine.

3.4 Additional Information

LCC noted that lung cancer is the leading killer of all cancers in Canada, and while the five-year net survival rate is still very low (19%), there have been improvements in the survival and quality of life of lung cancer patients. Targeted therapies have allowed patients to be functional and independent as a result of improved drug administration and manageable side effects; therefore, survival rates and quality of life has improved compared to traditional chemotherapy. Access to such treatments has extended the lives of patients like RP who was diagnosed in 2017 and given 10 days to live but is currently stable and lives a good new "normal."

Overall, LCC indicated that entrectinib is worth considering as it provides outcomes that align with patient values. LCC specified that the goal of cancer treatment is to provide the right drug for the right target and person. Notably, entrectinib not only personalizes the treatment but also addresses CNS presentations and allows patients to live well, achieve new life milestones, and spend more time with family and loved ones. There are a number of approved targeted forms of treatment for other molecular driven cancers such as EGFR and ALK NSCLC; thus, patients with the ROS-1 mutation should also be given the same opportunities.

LCC stated that there may be uncertainty regarding the need for another option considering the small percentage of NSCLC patients with this particular mutation; however, there is still an unmet need. With the likelihood of CNS involvement at diagnosis or post-treatment, which is a frequent cause of morbidity and mortality, entrectinib is a viable option that addresses this need. First-line crizotinib is currently still in pricing negotiations and studies have shown that it may not penetrate the blood brain barrier. The LCC also mentioned the unlikelihood of a phase III trial being conducted soon; accordingly, they ask that a conditional approval be granted as this would allow the collection of third-line data while providing access to patients and to allow for the collection of real-world evidence. Additionally, LCC noted that with the addition of another option into pricing negotiations, entrectinib can introduce market-place competition, which could help manage costs in the Canadian publicly funded healthcare system. LCC recommends a collaborative effort between the manufacturer and government to devise innovative pricing solution.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary
Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing of treatment and place in therapy for entrectinib

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities
- Number of patients requiring and access to ROS-1 testing

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that the standard of care for first-line treatment of patients with ROS-1 mutation positive locally advanced or metastatic NSCLC is crizotinib but this is not universally funded at this time. If first line crizotinib is not available, then chemotherapy (e.g., cisplatin plus pemetrexed) would be an option.

Patients with ≥50% tissue expression of PD-L1 are also eligible to receive first-line pembrolizumab, while the latter combined with chemotherapy is reimbursed in most provinces for all patients regardless of PD-L1 expression. However, tumours must not harbor a sensitizing EGFR mutation or ALK translocation. PAG would like confirmation that the same would apply for ROS-1 rearrangement in practice and that first-line pembrolizumab should not be used in this population.

4.2 Eligible Patient Population

The pivotal trials of entrectinib are phase I studies (STARTRK-1/ALKA-372-001) in adult patients with locally advanced or metastatic cancer targeting NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations and STARTRK-2 for the treatment of patients with solid tumors harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK gene rearrangements. PAG noted that these trials included patients with an ECOG 0-2 and is seeking guidance on the use of entrectinib in patients with poor performance status (i.e., ECOG >2).

If recommended for reimbursement, PAG noted that the following groups of patients would need to be addressed on a time-limited basis:

- Patients with ROS-1 positive NSCLC who are currently receiving either first-line chemotherapy, PD-1 inhibitors, or crizotinib

PAG remarked that the reimbursement request is for first-line treatment of patients with ROS1- positive locally advanced or metastatic non-small cell lung cancer. Since entrectinib was approved by Health Canada for ROS-1 positive advanced or metastatic NSCLC not previously treated with crizotinib, PAG noted that there may be pressure to reimburse the drug for this indication beyond first line, should the recommendation align with the sponsor-requested criteria. Patients with NTRK+ or ALK+ tumours as well as treatment in the adjuvant setting (in the event there is reflex ROS-1 testing) would be considered out of scope of the current review.

4.3 Implementation Factors

Entrectinib is administered once daily which is an enabler to implementation. PAG noted the recommended dose is 3 capsules daily which may represent pill burden.

Additional health care resources (e.g., frequent clinic visits while patients are on therapy) are required for monitoring adverse effects and tolerability with entrectinib. Increased pharmacy time would be required for dispensing entrectinib.

Entrectinib potentially represents an additional line of therapy so is an added cost. Due to the small number of patients with ROS-1 mutations, wastage could occur.

Entrectinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm place in therapy with entrectinib and optimal sequencing with chemotherapy, crizotinib, and PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab) for ROS-1 NSCLC:

- Is entrectinib the preferred first-line agent for ROS1 mutations?
- Can entrectinib be used when a ROS-1 positive tumour acquires a mutation conferring resistance to crizotinib, or vice versa?
- Is there evidence to inform use of entrectinib in patients with ROS-1 positive NSCLC who experience CNS disease progression on first-line crizotinib? Would entrectinib be used after crizotinib or other ROS-1 targeted agents but before subsequent therapies? Or would entrectinib be used more in later lines or last resort therapy?

PAG is seeking clarity on whether crizotinib and entrectinib are therapeutically equivalent for the treatment of ROS-1 mutated NSCLC.

PAG is seeking confirmation that patients who started chemotherapy, or PD-1 inhibitors while waiting for ROS-1 test results be switched to entrectinib should the results be positive. PAG is also seeking confirmation that patients cannot have both ROS-1 and NTRK mutations.

4.5 Companion Diagnostic Testing

PAG noted that ROS-1 is not routinely available in all provinces. PAG members noted there is no formalized testing process or funding in place for ROS-1 in some jurisdictions. Health care resources and coordination to conduct the ROS-1 testing in the first-line setting will be required. The significant increase in costs for ROS-1 testing may be a barrier to implementation.

PAG had concerns related to:

- the turnaround time for ROS-1 testing
- whether all NSCLC patients are required to be tested for ROS-1
- how testing is performed (i.e., through IHC or FISH or other methods)
- as patients are currently tested for EGFR, PD-L1, and ALK in the first-line setting, whether there will enough tissue sample to test for ROS-1 as the fourth test

Therefore, the number of patients requiring ROS-1 testing and access to ROS-1 testing may be a barrier to implementation.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of entrectinib (Rozlytrek) for the first-line treatment of adult patients with ROS-1 positive locally advanced or metastatic NSCLC: two clinicians provided input on behalf of Cancer Care Ontario (CCO) Lung Drug Advisory Committee (DAC) and six clinicians provided input on behalf of LCC. Overall, it was noted that entrectinib is an orally administered targeted therapy that demonstrates superior tolerability and effectiveness compared to chemotherapy and immunotherapy, which are the current treatment options for ROS-1 NSCLC. Namely, chemotherapy is contraindicated in poor performance status patients (e.g., frailer patients, patients with co-morbidities, or patients with CNS metastases) while immunotherapy has limited activity in tumours harbouring driver mutations (e.g., ROS-1, EGFR, and ALK) and exhibit a potential for significant autoimmune toxicities. As entrectinib is a selective TKI inhibitor, a companion diagnostic test is required to identify ROS-1 rearrangements; this test is currently not funded in Ontario and is variably implemented across Canada. The LCC clinicians highlighted that entrectinib would address the clinical unmet need for all ROS-1 tumour types, not exclusively for NSCLC, including less common ROS-1 rearrangements in glioblastoma multiforme, cholangiocarcinoma, and colorectal, gastric, and ovarian cancers. Moreover, the CCO clinicians stated that it would be extremely rare for patients to have both ROS-1 and NTRK mutations as the TRK fusions are already so rare, and the LCC clinicians stated that it is generally felt that these genetic aberrations are mutually exclusive.

Both inputs supported up-front administration of targeted therapy (entrectinib or crizotinib) followed by chemotherapy then immunotherapy (PD-1 inhibitors); the CCO clinicians specified that entrectinib should be the first TKI a patient receives and not necessarily as first-line treatment (i.e. patients may receive treatment prior to determining ROS-1 status). Accordingly, the clinicians supported the practice of switching to entrectinib from chemotherapy upon confirmation of a patient's ROS-1 re-arrangement status. Moreover, the clinicians felt that entrectinib is either as effective or slightly more effective than crizotinib; however, no robust direct comparison exists (e.g. RCT). Notably, direct comparisons may not be possible due to the rarity of ROS-1 gene re-arrangements. Nevertheless, both inputs specified that crizotinib is less CNS-penetrant than entrectinib; therefore, entrectinib would be preferred for patients with CNS metastases. However, it was noted that there is no direct evidence to inform the use of entrectinib in ROS-1 positive NSCLC patients who experience CNS disease progression on crizotinib. Additionally, both inputs indicated that there is no strong evidence to support the use of PD-1 or PD-L1 inhibitors following entrectinib; although, the LCC clinicians stated that immunotherapy could be considered after entrectinib, other ROS-1 inhibitors, and chemotherapy since ROS-1 patients were not excluded from immunotherapy trials unlike EGFR- and ALK positive patients. Further, when asked if patients with ROS-1 mutations can be given first line pembrolizumab if their tumour exhibits high PD-L1 expression, all clinicians indicated a preference for targeted agents over immunotherapy. Of note, the CCO clinicians specified that, it is difficult to determine optimal sequencing for ROS-1 positive NSCLC since the supporting data for sequencing is in TKI naïve patients.

Overall, the clinicians noted that entrectinib may address the clinical unmet need for more tolerable and effective therapies for ROS-1 positive NSCLC; namely, the need for a CNS-penetrant and effective agent. Thus, both inputs expressed support for making entrectinib available to facilitate access to multiple treatment options for ROS-1 positive NSCLC. The LCC clinicians specified that entrectinib should be made available since multiple EGFR inhibitors have been approved (e.g., gefitinib, afatinib, dacomitinib, and osimertinib); thus, ROS-1 positive NSCLC patients should have access to targeted therapies for ROS-1 mutations as well. Additionally, they highlighted that entrectinib should be available despite the recent conditional positive recommendation of crizotinib because it is common for patients to develop side effects to targeted agents. Thus, the availability of entrectinib as a second targeted option is particularly advantageous since it may be also used to treat primary brain tumours and brain metastases.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

The CCO and LCC clinicians stated that chemotherapy is currently the standard of care for first-line treatment of advanced NSCLC. Crizotinib is another treatment option that is currently not funded; therefore, crizotinib may only be available for patients with private insurance.

The LCC clinicians specified that chemotherapy for first-line treatment of advanced NSCLC generally involves cytotoxic platinum-doublet chemotherapy. Chemotherapy is contraindicated in frailer patients and those with significant co-morbidities and is unlikely to

be effective for patients with CNS metastases. Accordingly, only a minority of patients receive platinum-doublet chemotherapy since it is not usually administered to poor performance status patients. Furthermore, the LCC clinicians noted that recent RCTs support the use of immune checkpoint inhibitors as monotherapy in the first-line setting for highly positive PD-L1 tumours and in an all comers population (regardless of PD-L1 status); in combination with chemotherapy in the first-line setting; or as monotherapy in the second-line setting. The clinicians noted that ICIs are associated with better survival, more durable responses, and fewer side effects compared to chemotherapy; however, the effect is blunted in tumours driven by one or few key mutations. Namely, ICIs are associated with a poor outcome even in EGFR- and ALK positive NSCLC patients whose tumours exhibit strong PD-L1 positivity; thus, it is reasonable to expect minimal benefit from immunotherapy in ROS-1 positive NSCLC patients.

5.2 Eligible Patient Population

The CCO and LCC clinicians felt that the trial criteria are relevant and may be applied to clinical practice. However, the CCO clinicians specified that entrectinib should only be used in the metastatic setting; for instance, not in adjuvant settings. Additionally, the CCO clinicians stated that entrectinib potentially fills an unmet clinical need.

The LCC clinicians stated that patients with CNS progression following treatment with crizotinib may benefit from entrectinib as entrectinib was designed to cross the blood-brain barrier to target primary CNS tumours and CNS metastases. Namely, this is extrapolated from the thought that crizotinib is less CNS-penetrant and the treatment experience of ALK positive NSCLC patients. Further, the LCC clinicians specified that entrectinib would help address the unmet clinical need for ROS-1 positive NSCLC and for other less common tumour types harbouring the ROS-1 gene fusion. Rare subgroups of ROS-1 re-arrangements are poorly served by chemotherapy and immunotherapy and include glioblastoma multiforme, cholangiocarcinoma, and colorectal, gastric, and ovarian cancers.

5.2.1 Implementation Question—Can patients have both ROS-1 and NTRK mutations?

The CCO clinicians stated that the "*TRK fusions are so rare that it is probably extremely, extremely rare*" for patients to have both ROS-1 and NTRK mutations. Similarly, the LCC clinicians stated that it is generally felt that these genetic aberrations are mutually exclusive; this assumption justifies the sequential, single gene testing that is currently most widely practiced in Canada. However, the LCC clinicians noted that as NGS panel testing becomes more common, it is likely that a broad range of mutations in a single cancer will be discovered. Thus, over the next few years, more robust data on simultaneously occurring driver mutations may inform treatment algorithms.

5.2.2 Implementation Question—Can patients with ROS-1 mutations be given first-line pembrolizumab if the tumour expresses high PD-L1?

Both clinician inputs indicated a preference for targeted agents over immunotherapy such as pembrolizumab. Namely, the CCO clinicians stated that targeted agents are preferred over immunotherapy if a patient has access to targeted agents. The LCC clinicians noted that most medical oncologists have great reservations about administering immunotherapy to NSCLC patients with any driver mutation including ROS-1. They elaborated that immunotherapy is generally less effective in driver mutation-dependent cancers (e.g., EGFR-, ALK-, and ROS-1- positive NSCLC) as it is assumed that a lack of neo-antigenicity limits the immunogenicity of the cancer cells; thus, reducing the ability of the immune system to act on the cancer cells. Therefore, checkpoint blockade inhibition in driver mutation-dependent cancers have been associated with worse prognoses despite some of these cancers expressing high levels of PD-L1. Accordingly, the LCC clinicians stated that these patients should be treated with targeted therapies such as entrectinib or crizotinib and that immunotherapy should only be considered after treatment failure with targeted therapy and chemotherapy.

5.3 Relevance to Clinical Practice

The clinicians providing input on behalf of CCO did not have experience administering entrectinib. They stated that having multiple ROS-1 inhibitors (sequentially) is more important than having two front-line treatments and that entrectinib would essentially replace crizotinib if it is funded. Entrectinib appears to be slightly better than crizotinib; however, there is no direct comparison. Overall, the clinicians expressed their support of having a greater number of treatment options for patients.

Clinicians providing input on behalf of LCC had experience administering entrectinib. They noted that the general international consensus among thoracic medical oncologists is that targeted therapy such as entrectinib should be administered in the first-line setting. Namely, they specified that entrectinib should be a first-line treatment option for ROS-1 positive NSCLC patients presenting with de novo CNS metastases. The LCC clinicians stated that given a choice, they would choose to administer entrectinib for ROS-1 positive NSCLC and they support making entrectinib available. They further alluded to early phase trials of entrectinib exhibiting superior tolerability over chemotherapy and immunotherapy. Namely, chemotherapy and immunotherapy are associated with significant toxicity that limits administration to patients with poor performance status (e.g., frailer patients, patients with co-morbidities, or patients with CNS metastases) and potential significant autoimmune toxicities, respectively. Additionally, the trial data exhibited greater durability of disease control of entrectinib over chemotherapy. Overall, research has demonstrated that targeted therapies are more effective than cytotoxic chemotherapy, associated with less toxicity, and provide a better quality of life. Moreover, the LCC and CCO clinicians felt that entrectinib appears to be at least as effective and maybe slightly better than crizotinib, which recently received a conditional positive recommendation from pERC. Namely, entrectinib exhibits a slightly higher response rate, slightly longer response duration, and similar PFS compared to crizotinib (for further detail, please refer to the data reported on the PROFILE 1001 and Ox Onc trials in the pCODR clinical guidance report and recommendation for the review of crizotinib for ROS-1 positive advanced NSCLC-10151).

5.4 Sequencing and Priority of Treatments with New Drug Under Review

5.4.1 Is there evidence to support the optimal sequencing of entrectinib with chemotherapy, crizotinib, and PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab) for ROS-1 NSCLC?

The CCO clinicians stated that crizotinib or entrectinib should be administered first followed by chemotherapy and then a PD-1 inhibitor (immunotherapy); however, they specified that ultimately the sequence depends on when the ROS-1 status is determined. Theoretically, entrectinib would be replacing crizotinib in the first-line setting; thus, being administered as a patient's first TKI and not necessarily as first-line therapy for NSCLC. For instance, if a patient's ROS-1 status was determined after initiating chemotherapy, entrectinib would be the patient's first TKI but not first-line therapy for NSCLC. Of note, the CCO clinicians stated that the supporting data is from TKI naïve patients; thus, it is hard to extrapolate sequencing from such data.

Similarly, the LCC clinicians stated that there is insufficient data to definitively guide their practice in these settings; furthermore, large RCTs to better define treatment algorithms will not likely be conducted due to the rarity of ROS-1 gene re-arrangements among NSCLC patients. Nevertheless, one clinician, who has had first-hand experience successfully administering entrectinib for a mammary analogue secretory carcinoma patient, specified that administration of entrectinib would relegate chemotherapy to the second- or third-line setting. Further, immunotherapy would only be offered following failure of treatment with chemotherapy because immunotherapy has limited effectiveness in patients whose tumours harbour a driver mutation.

5.4.2 In what clinical scenarios (e.g., CNS involvement) would entrectinib or crizotinib be the preferred treatment for ROS-1 NSCLC?

The CCO clinicians stated that entrectinib appears to have good CNS penetration whereas crizotinib does not. Therefore, entrectinib may be preferred for patients with CNS disease but its administration will also depend on toxicities and tolerability.

Overall, the LCC clinicians indicated that entrectinib would be the preferred treatment over crizotinib for ROS-1 positive NSCLC patients with CNS metastases because entrectinib appears to be more CNS-penetrant. Namely, they stated that targeted therapy that crosses the blood-brain barrier is particularly necessary since RCT data suggests that whole-brain radiotherapy does not affect survival outcomes. Similarly, traditional chemotherapy does not reliably cross the blood-brain barrier as anti-tumour activity is only described anecdotally. Entrectinib has shown promising anti-tumour activity in the CNS; on the other hand, crizotinib is thought to be less CNS-penetrant. Among ALK positive NSCLC patients, studies suggest that crizotinib does not penetrate the blood-brain barrier well, which is thought to be due to the fact that crizotinib is a substrate of the P-glycoprotein and human adenosine triphosphate-binding cassette subfamily efflux transporters.

5.4.3 Is there evidence to inform use of entrectinib in patients with ROS-1 positive NSCLC who experience CNS disease progression on crizotinib? Would entrectinib be used after crizotinib or other ROS-1 targeted agents but before subsequent therapies? Or would entrectinib be used more in later lines or last resort therapy?

The CCO clinicians stated that the data for entrectinib is for TKI naïve patients; thus, entrectinib would not be administered after crizotinib. Additionally, they noted that entrectinib appears to have more CNS activity and potentially less toxicity than crizotinib. However, if entrectinib therapy failed for a patient they may get lorlatinib. The LCC clinicians simply stated that there is no evidence to inform the use of entrectinib in ROS-1 positive NSCLC patients who experienced CNS disease progression on crizotinib.

5.4.4 Is there any evidence to support the use of PD-1 or PD-L1 inhibitors after entrectinib?

The CCO clinicians stated that there is probably a very small number of patients from other trials but nothing substantial to support the use of PD-1 or PD-L1 inhibitors after entrectinib.

The LCC clinicians stated that, arguably, immunotherapy could be considered after entrectinib, other ROS-1 inhibitors, and chemotherapy since ROS-1 patients were not explicitly excluded from many immunotherapy trials unlike the EGFR- and ALK-patients. However, as they mentioned, there is little evidence exhibiting the efficacy of immunotherapy in any of the oncogene driven NSCLC sub-types.

5.5 Companion Diagnostic Testing

The CCO clinicians highlighted that companion diagnostic testing for the ROS-1 mutation will require funding in Ontario. Correspondingly, the LCC clinicians stated that routine ROS-1 testing in non-squamous NSCLC has not been uniformly implemented across the country; however, guidelines recommend that all patients with advanced non-squamous NSCLC be tested at diagnosis for ROS-1 rearrangements. Presently, FISH testing with a ROS-1 break apart probe is the gold standard for detecting ROS-1 rearrangements; nevertheless, the Canadian ROS (CROS) initiative is currently validating IHC testing for ROS-1 translocations in NSCLC tumour samples across 14 Canadian centres. In the opinion of the LCC clinicians, ROS-1 testing for NSCLC should be routine within the next five years given the increasing number of targeted therapies, decreasing costs of NGS testing, introduction of private genomic testing, and greater demand and access to more routine tumour genomic profiling (i.e., the CROS initiative and advancement and increasing availability of new technologies). Of note, the LCC clinicians did not comment about routine ROS-1 testing for squamous NSCLC patients.

5.6 Implementation Questions

5.6.1 Treatment switching—Can patients who started chemotherapy while waiting for ROS-1 test results be switched to entrectinib should the results be positive?

The CCO and LCC clinicians support the practice of patients switching from chemotherapy, that was initiated while waiting for ROS-1 test results, to entrectinib upon receiving confirmation of ROS-1 status. The LCC clinicians highlighted that ideally, with upfront routine ROS-1 testing, patients should be offered entrectinib as first-line treatment. Additionally, the timeliness of the companion diagnostic testing is critical to ensure that patients are not unnecessarily subjected to a more toxic therapy (chemotherapy) while a better tolerated agent is available.

5.7 Additional Information

The LCC clinicians stated that entrectinib should be available as a treatment option for ROS-1 positive NSCLC since multiple EGFR inhibitors such gefitinib, afatinib, dacomitinib, and osimertinib have been approved for EGFR positive NSCLC. Furthermore, although the approval of crizotinib provides a therapeutic option for ROS-1 positive NSCLC patients, if funded, the availability of entrectinib is still important for the following reasons:

- Treatment experience with small molecular inhibitors of EGFR and ALK to date demonstrate that it is not uncommon for patients to experience side effects from these agents, which necessitates a change to another therapeutic molecule of the same class. Thus, a second ROS-1 inhibitor provides that option.
- Entrectinib was specifically designed to cross the blood-brain barrier in an effort to address both primary brain tumors and brain metastases in patients. As observed in ALK positive NSCLC patients, using a more CNS-penetrant drug in the first-line setting improves survival; this may also be the case with entrectinib for ROS-1 patients.

Thus, gathering real world evidence as more ROS-1 patients are treated may highlight subtle differences in activity between ROS-1 inhibitors to provide a clearer understanding of how these agents may best be used or sequenced.

6 Systematic Review

6.1 Objectives

The objective of this review is to evaluate the efficacy and safety of entrectinib as monotherapy for the first-line treatment of adult patients with ROS-1 positive locally advanced or metastatic NSCLC.

Supplemental Questions and Comparison with Other Literature most relevant to the CADTH review and to the PAG were identified while developing the review protocol and are outlined in Section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 7. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 7: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs† In the absence of RCT data, fully published clinical trials* investigating the safety and efficacy of entrectinib for ROS-1 positive NSCLC will be included.	Adult patients (aged ≥18 years) with histologically or cytologically verified locally advanced or metastatic NSCLC positive for ROS-1 rearrangements. Subgroups: • Brain metastasis at baseline (Yes vs. No)	Entrectinib monotherapy	• Crizotinib • Chemotherapy (platinum + pemetrexed, with pemetrexed maintenance	Efficacy: • **OS** • PFS • ORR • Duration of response • Clinical benefit rate • Time to treatment failure • CNS Response rate Safety: • AEs • SAEs • WDAE **Patient-reported outcomes/ QoL**

AE = adverse events; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; QoL = health-related quality of life; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

†Including trials conducted as part of a master protocol (basket, umbrella, or platform trials)

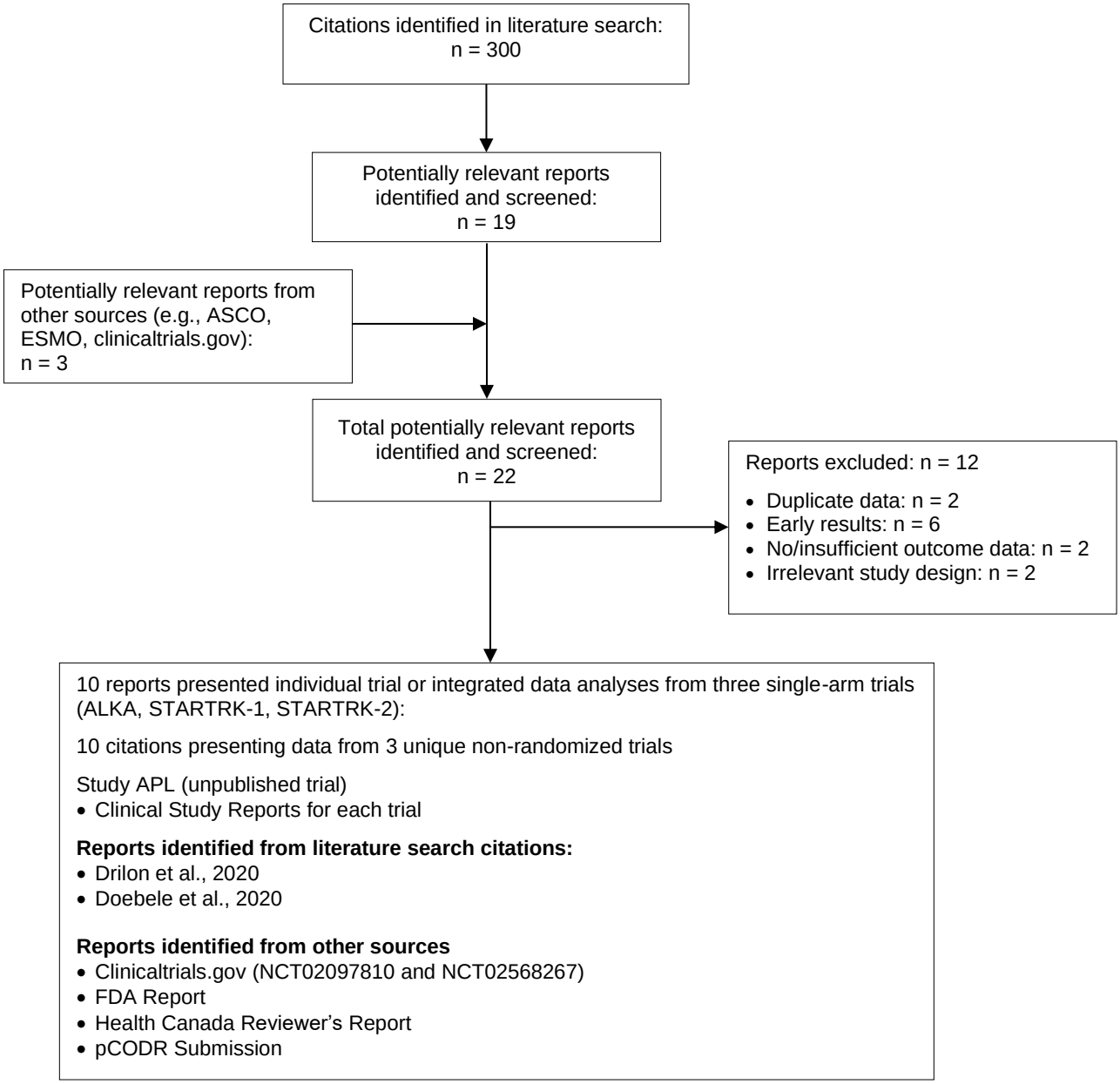
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 22 potentially relevant citations that were identified, 10 reporting data from three non-randomized clinical trials were included in the CADTH systematic review[2,3,11,21-27] and 13 studies were excluded. Studies were excluded because they were: duplicates, had early results, had no/ insufficient outcome data, or had an irrelevant study design.

Figure 1: Flow Diagram for Study Selection



6.3.2 Summary of Included Studies

This CADTH systematic review included three open-label single-arm trials of entrectinib in adult patients with advanced or metastatic solid tumours (ALKA, STARTRK-1 and STARTRK-2). Two trials were completed Phase I studies (ALKA and STARTRK-1); whereas one was an ongoing Phase II basket study (STARTRK-2).[28]

The data submitted by the sponsor in support of the CADTH reimbursement request is based on a pooled analysis (integrated efficacy set) of efficacy from three non-comparative adult clinical trials (ALKA, STARTRK-1, and STARTRK-2). The safety data were pooled across four trials (ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG a small pediatric phase I/Ib trial). Of note, the patient population from the STARTRK-NG does not directly provide evidence to support the CADTH reimbursement indication, which is limited to adult patients. The pooled safety data included 16 pediatric patients from this trial.[3,11]

The sponsor noted that given the rarity of ROS-1 positive NSCLC, the integrated analyses served to maximize the number of patients available for analyses. According to the sponsor, the integrated analysis was agreed to by the Federal Drug Administration (FDA) and European Medicines Agency (EMA).[3]

This report provides brief descriptions of the three individual studies (ALKA, STARTRK-1, and STARTRK-2) that met the inclusion criteria of the CADTH systematic review and will report detailed methods and results for the pooled efficacy and safety analyses. The detailed characteristics are provided in Table 8 and select quality characteristics are in Table 9.

6.3.2.1 Detailed Trial Characteristics

Table 8: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: (ALKA) ALKA-372-001 (GO40783)[25] EudraCT 2012-000148-88 Characteristics: (Open-label, single-arm, multicenter phase 1 dose escalation study) **Sample size**: 57 **Included in ROS-1 integrated efficacy set**: 9[11] **Number of centres and number of countries:** 2 sites in Italy **Patient Enrolment Dates** October 26, 2012 – March 27, 2018[25] **Data cut-off** (inclusion into integrated efficacy set): May 31, 2018 October 31, 2018 May 1, 2019 **Trial status:** Complete[28] **Funding:** Hoffman-La Roche Ltd.	**Key Inclusion Criteria:** • Adults ≥ 18 years of age • Histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumours with TRKA, TRKB, TRKC, ROS-1, or ALK genetic alterations in patients for whom no alternative effective standard therapy was available • Availability of tumour tissue • Prior cancer therapy accepted, except TRK, ROS-1, or ALK (non-NSCLC patients only) inhibitors in patients with tumours that harbor those respective molecular alterations • Other than above, prior therapy allowed and at the time of treatment start, at least 4 weeks must have elapsed or in the absence of toxicity, 5-half lives, since completion of prior therapy (at least 6 weeks for nitrosureas, mitomycin C, and liposomal doxorubicin) • Prior radiotherapy allowed provided no more than 25% of bone marrow reserve was irradiated • Controlled asymptomatic CNS involvement (use of seizure prophylaxis allowed if on non-EIAEDs or steroid use if at stable dose for at least 2 weeks at ≤4 mg/day dexamethasone or equivalent) • Resolution of acute toxic effects excluding alopecia of prior anticancer therapies according to NCI CTCAE v.4.03 grade ≤1 or to the baseline laboratory values • ECOG PS ≤ 2 • Life expectancy of at least 3 months **Key Exclusion Criteria:** • Enrolment in another therapeutic clinical trial • Active second malignancy except for adequately treated basal or squamous cell skin cancer and/or cone-biopsied in situ carcinoma of the cervix uteri	Entrectinib monotherapy administered orally as capsules in the following 3 dosing schedules until RP2D determination (doses ranged from 100-1600 mg/m^2):[11] **Schedule A:** • Fasted condition • 4-week cycles: 4 days on/3 days off for 3 weeks followed by 7 days of rest • QD dosing **Schedule B:** • Fed condition • 4-week cycles: continuous daily dosing • QD dosing **Schedule C:** • Fed condition • 4-week cycles: 4 days on/ 3 days off for 28 days	Primary:[11] • First cycle DLT's and MTD administered in three different dosing schedules (Schedule A, B, and C) Secondary: • Safety • PK • Anti-tumour activity

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	and/or superficial bladder cancer; other prior cancers must be disease-free for ≥5 years • Major surgery other than diagnostic surgery within 4 weeks prior to treatment • MI, unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, pulmonary embolism, DVT within the past 6 months • Prolonged QTc interval (> 450 ms) • Risk factors for torsade de pointes • Known active infections (bacterial, fungal, viral including HIV positivity) • Active GI disease/malabsorption syndromes or documented GI ulcer • Known interstitial lung disease or interstitial fibrosis		
Study: STARTRK-1[29] RXDX-101-01 NCT02097810 **Characteristics:** Multicentre, open-label, single-arm, phase 1 study **Sample size:** 76 **Included in ROS-1 integrated efficacy set**: 7 **Number of centres and countries:** 10 sites: one hospital and seven cancer centres in three countries (USA, Spain and South Korea).[2] **Patient Enrolment Dates:** August 7, 2014 – May 10, 2018[2]	**Key Inclusion Criteria:**[27] • Adults ≥ 18 years of age • Histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumours that have a NTRK1, NTRK2, NTRK3, ROS-1, or ALK molecular alteration • Measurable disease according to RECIST 1.1 • Prior treatment allowed including radiotherapy and drugs (crizotinib, ceritinib, and investigational drugs) • Controlled asymptomatic CNS involvement • Resolution of acute toxic effects (excluding alopecia) of prior anticancer therapies according to NCI CTCAE v.4.03 grade ≤1 • ECOG PS ≤ 2 • Life expectancy of at least 3 months **Key Exclusion Criteria:** • Participation in another therapeutic clinical trial • Prior treatment with entrectinib • History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds)	**Dose escalation:**[11] • Starting entrectinib monotherapy dose (capsules taken orally) of 100 mg/m^2 once daily, in fed condition, for 28 consecutive days in repeated 4-week cycles (other doses tested: 200 mg/m^2, 400 mg/m^2, or 600 or 800 mg once daily) • 3+3 enrolment scheme • Patients with CNS disease who have been on study for at least 2 cycles of treatment (i.e., 8 weeks) with a BR of SD as per RECIST 1.1 and without treatment-related grade ≥2 AEs, dose escalation to 800 mg QD is allowed	**Dose escalation:**[11] *Primary:* • First cycle DLTs, MTD, and RP2D *Secondary:* • Safety (AE type, severity, timing, ECG, and lab abnormalities) • PK • Antitumour activity measured by tumour response (ORR, DOR, PFS, and OS) • Biomarker evaluation • PD Dose expansion: *Primary:* • ORR defined as the proportion of patients with

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Data cut-off dates (inclusion into integrated efficacy set): May 31 2018 October 31 2018[11] May 1, 2019 **Trial status:** Complete[28] **Funding:** Hoffman-La Roche Ltd.	• Risk factors for torsade de pointes (e.g. family history of long QT syndrome). • Known active infections (bacterial, fungal, viral including HIV positivity) • Gastrointestinal disease or malabsorption syndromes (e.g. Crohn's disease, ulcerative colitis, or short gut syndrome) • Interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis • Peripheral neuropathy ≥ Grade 2	**Dose expansion:** 600 mg flat dose of entrectinib, orally, QD for 28 consecutive days in repeated 4-week cycles	complete response (CR) or partial response (PR) *Secondary:* • PFS • OS • CBR • DOR • Intracranial tumour response in patients with CNS disease • Safety and tolerability of entrectinib • Biomarker evaluation • PD • PK
Study: STARTRK-2[30] RXDX-101-02 NCT02568267 **Characteristics:** Multicentre, open-label, single-arm, phase 2 basket study **Sample size:** 206 **Included in ROS-1 integrated efficacy sets:** • 37*[11] (efficacy evaluable analysis set, total N = 53); • 78 (expanded efficacy evaluable analysis set total n = 94) **Number of centres and countries:**[2] More than 150 sites (cancer and medical centres, research institutes, hospitals, and	**Key Inclusion Criteria:**[26] • Adults ≥ 18 years of age • Histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumours that have a NTRK1, NTRK2, NTRK3, ROS-1, or ALK gene rearrangement (including ALCL) • Archival or fresh tumour tissue available for confirmation at a CLIA-certified lab • Measurable or evaluable disease • CNS involvement including leptomeningeal carcinomatosis, which was either asymptomatic or previously treated and controlled • Prior anti-cancer allowed (excluding TRK, ROS-1, and ALK inhibitors for patients with the respective gene rearrangements).[26] Note: prior treatment with crizotinib was permitted only in ALK-or ROS-1-rearranged NSCLC patients presenting with CNS-only progression • ≥2 weeks or 5 half-lives, whichever was shorter, must have elapsed since prior chemotherapy or small molecule targeted therapy, respectively	Entrectinib monotherapy administered orally as capsules at a dose of 600 mg QD continuously for 28 days (4-week cycles)[11] Note: Patients with CNS disease who have been on study for at least 2 cycles of treatment (i.e., 8 weeks) with a BR of SD as per RECIST version 1.1 and without treatment-related grade ≥2 AEs, dose escalation to 800 mg QD was allowed	**Primary:**[11] • ORR assessed by BICR in each patient population basket of solid tumours (NTRK 1/2/3, ROS-1, or ALK gene rearrangement) **Secondary:** • DOR assessed by BICR in each patient population basket of solid tumours • TTR assessed by BICR in each patient population basket of solid tumours • CBR assessed by BICR in each patient population basket of solid tumours • Intracranial response: CNS-PFS in patients with measurable CNS disease at

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
universities across 15 countries: Australia, Belgium, France, Germany, Hong Kong, Italy, Japan, South Korea, Netherlands, Poland, Singapore, Spain, Taiwan, United Kingdom, and US) **Patient Enrolment Dates** November 19, 2015 to March 2026[28] **Data cut-off date** (inclusion into integrated efficacy set): May 31, 2018 October 31, 2018 May 1, 2019 **Estimated completion date:** December 2, 2024[26] **Funding** Hoffman-La Roche Ltd.	• ≥4 weeks since completion of antibody-directed therapy at the start of entrectinib • Prior radiotherapy allowed if >14 days since final treatment • ECOG PS ≤ 2 and minimum life expectancy of 4 weeks • Adequate organ function • Ability to swallow entrectinib intact **Key Exclusion Criteria:** • Current participation in another therapeutic clinical trial • History of previous cancer that would interfere with the determination of safety or efficacy of entrectinib • Incomplete recovery from any surgery • History of recent (within 3 months) symptomatic CHF or ejection fraction ≤50% observed during screening • History of non-pharmacologically induced prolonged QTc interval • History of risk factors for torsade de pointes • Peripheral neuropathy grade ≥2 • Known active infections • Active GI disease/malabsorption syndromes • Known interstitial lung disease, interstitial fibrosis, or history of TKI induced pneumonitis.		baseline, assessed by BICR using RANO or RANO-BM as applicable) • PFS • OS • Safety and tolerability • PK • Effect of entrectinib on ventricular repolarization • HRQoL
Integrated Analysis (ALKA + STARTRK-1 + STARTRK-2) **Sample size:** • 53 (Primary ROS-1 NSCLC Efficacy-Evaluable Analysis Set) • 94 (Overall ROS-1 NSCLC Efficacy-Evaluable Analysis Set) • 355 (Overall Safety Set) • 504 (Expanded safety Set)	Patients had to meet the following criteria to be included in the ROS-1 NSCLC efficacy population for the integrated analysis: • Have tumours that harbor a ROS-1 gene fusion • Received at least one dose of entrectinib • Have locally advanced or metastatic NSCLC • Not treated previously with a ROS-1 inhibitor (e.g., crizotinib) • ECOG≤2	Entrectinib monotherapy administered orally as capsules at a dose of 600 mg QD continuously for 28 days (4-week cycles)[11]	**Primary:**[11] • ORR assessed by BICR in each patient population basket of solid tumours (NTRK 1/2/3, ROS-1, or ALK gene rearrangement) **Secondary:** • DOR • TTR • CBR

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Data cut-off dates: [2] May 31, 2018;[25] October 31 2018;[11] May 1 2019;[3] Estimated completion date: data cut-off dates for post marketing requirements to occur in future[28] **Funding** Hoffman-La Roche Ltd.			• Intracranial response: CNS-PFS in patients with measurable CNS disease at baseline, assessed by BICR using RANO or RANO-BM as applicable) • PFS • OS • Safety and tolerability • PK • Effect of entrectinib on ventricular repolarization • HRQoL

AE = adverse event; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; BICR = blinded independent central review; BM = brain metastases; BR = best response; BSA = body surface area; CBR = clinical benefit rate; CHF = coronary heart failure; CLIA = clinical laboratory improvement amendments; CNS = central nervous system; CR = complete response; CTCAE = common terminology criteria for adverse events; DCR = disease control rate; DLT = dose-limiting toxicities; DOR = duration of response; DVT = deep vein thrombosis; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EIAEID = enzyme-inducing anti-epileptic drug; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IEA = ROS1 Integrated Efficacy Analysis; GI = gastrointestinal; MI = myocardial infarction; mg = milligram; ms = millisecond; MTD = maximum tolerated dose; NCI = national cancer institute; NSCLC = non-small cell lung cancer; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PD = progressive disease; PK = pharmacokinetics; PR = partial response; QD = once a day; RANO = response assessment in neuro-oncology; RANO-BM = RANO brain metastases; RECIST = response evaluation criteria in solid tumours; ROS-1 = receptor tyrosine kinase; RP2D = recommended Phase 2 dose; SD = stable disease; TKI = tyrosine kinase inhibitor; TRK = tyrosine kinase.

Sources:

Doebele et al., 2020[31]

Drilon et al., 2019[32]

FDA report, 2019[11]

Clinicaltrials.gov [NCT02568267[30], NCT02097810[29]]

Sponsor's response[28]

Note: *FDA analyses (May 31, 2018 data cut) excluded 2 patients receiving prior treatment with crizotinib

Table 9: Select quality characteristics of included studies of entrectinib in patients with ROS-1 fusion positive solid tumours

Trial	Treatment	Primary outcome[11]	Required sample size (as per sample size calculations)	Sample size*[11]	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
ALKA	Entrectinib	MTD	40[11]	57	N/A	N/A	N/A	N/A	No	No	Yes
STARTRK-1	Entrectinib	MTD, RP2D, and ORR	70*[11]	76	N/A	N/A	N/A	N/A	No	No	Yes
STARTRK-2	Entrectinib	ORR by BICR	62**[11]	206	N/A	N/A	N/A	N/A	No	No	Yes
Integrated Analysis	Entrectinib	ORR by BICR	50[11]	53	N/A	N/A	N/A	N/A	No	No	Yes

DLT = dose limiting toxicity; MTD = maximum tolerated dose; N/A = not applicable; ORR = objective response rate; RP2D = recommended phase 2 dose.

* 20 patients for dose escalation and 50 for dose expansion

** For the basket of ROS-1 fusion positive patients, up to 62 patients would be enrolled in the first stage, and if successful, an additional 90 patients would be enrolled in the second stage

a) Trials

ALKA-272-001 (ALKA)

Study design: ALKA was an open-label, multicentre, single-arm, phase 1 dose escalation trial in adult patients with advanced/metastatic solid tumours with NTRK 1/2/3, ROS-1, or ALK genetic alterations.[11] Patients were enrolled from October 26, 2012 to March 27, 2018.[25] The trial was conducted at two sites exclusively in Italy.[25] Three dosing schedules were investigated using a conventional "3+3" patient enrolment scheme.[11] All patients had to be observed for one cycle before subsequent patients were enrolled at the next (higher) dose level.[11]

Population: ALKA included adult patients ≥18 years of age with histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumours with ALK positive alterations or ALK negative patients with TRKA, TRKB, TRKC, or ROS-1 genetic alterations (later expanded to include ALK negative patients with TRKA or ROS-1 genetic alterations as per protocol amendment 5). The trial included patients for whom no alternative effective standard therapy was available, standard therapy was considered unsuitable, or had been refused (per protocol amendment 8) were eligible for the study. Other main eligibility criteria included: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2 and life expectancy of at least three months; and patients with controlled asymptomatic CNS involvement, in absence of therapy with anticonvulsant (as per protocol amendment 7), or in presence of therapy with non-enzyme-inducing anti-epileptic drugs (as per protocol amendment 8) or requiring steroids at stable dose (≤ 4 mg/day dexamethasone or equivalent) for at least two weeks. There were 11 entrectinib-treated patients with ROS1 positiveNCSLC[21] of which nine patients had ROS-1 positive fusion NSCLC[11] and were included in the integrated efficacy set.

Intervention: The study had an accelerated dose escalation phase per cohort until a predetermined level of toxicity occurred.[11] At that point, the dose escalation followed a modified Fibonacci scheme (50, 40, or 33% increments).[11] Patients received entrectinib orally in three different dosing regimens in 4-week cycles[11] (for details see Table 8). The dose level and schedule were assigned by the sponsor at the time of patient registration.[11] Dose escalation was continued until documented radiographic progression,

unacceptable toxicity, or withdrawal of consent.[2] Dose modifications were permitted for toxicities, and doses could be maintained or reduced after recovery from toxicities, if patients recovered within a maximum of two weeks.[11]

Study Endpoints: The primary endpoint was first cycle dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of entrectinib administered orally in each of the three schedules. Secondary endpoints were related to determining the safety profile of entrectinib, pharmacokinetics, and antitumour activity assessed via the objective tumour responses defined according to the RECIST criteria (version 1.1) every even (as per protocol amendment 1) or odd cycle (as per protocol amendment 6). For patients who continued treatment for 12 cycles or more, tumour response was measured every 3 cycles (as per protocol amendment 6). If more than 4 weeks had past from the last tumor imaging, this took place at the end of last treatment cycle.[11]

For the integrated analysis, data from ALKA was based on blinded independent central review (BICR) determinations of the objective response rate (ORR) using RECIST version 1.1. A point estimate and 95% confidence interval were calculated for the ORR based on the proportion of patients with confirmed complete response (i.e., a response that persisted >4 weeks from the initial response) or partial response. Tumour scans were retrospectively evaluated by the same BICR team using equivalent imaging review charters.[11] Duration of response (DOR) was estimated using the Kaplan-Meier method to calculate the median DOR and 95% confidence interval.

STARTRK-1

Study design: STARTRK-1 was a multicentre, open-label, single-arm phase 1 study of oral entrectinib in adult patients with a histologically or cytologically confirmed diagnosis of relapsed or refractory locally advanced or metastatic solid tumors for which no alternative standard therapy was available or standard therapy was considered unsuitable or intolerable.[11] In a dose escalation segment, NTRK1/2/3, ROS-1, or ALK molecular rearrangements were preferred, yet were not a requirement for patient eligibility.[11] For a dose expansion segment, only patients with the following were eligible to participate: NTRK gene rearrangements (fusions) previously treated with other TRK inhibitors, ALK gene rearrangements with 1198 resistance single-nucleotide polymorphism (SNP), ALK alternative transcription initiation (ALK^{ATI}), NTRK/ROS/ALK overexpression >6 (via RNA), activating splice variants, and other molecular alterations of interest, depending on biological rationale and after discussion with the sponsor.[11] Patients were enrolled from August 7 2014 to May 10 2018.[2] The trial was conducted in 11 sites: 9 sites in the USA, one hospital in Spain, and one centre in South Korea.[2] The trial included a dose escalation and dose expansion phase where molecular alterations were only required for enrolment in the dose expansion phase (NTRK1, NTRK2, NTRK3, ROS-1, or ALK by local testing). Dose escalation was investigated using a conventional "3+3" enrolment scheme with an accelerated titration design. Eligible patients enrolled in the dose expansion phase were grouped into molecularly-defined cohorts under a Simon's 2-stage (minmax) design determined by the type of molecular alteration harboured by the patient's tumour.[11]

Population: STARTRK-1 included adult patients ≥18 years of age with any histologically or cytologically confirmed advanced or metastatic tumours with a NTRK1, NTRK2, NTRK3, ROS1, or ALK molecular alterations by assay assessment.[27] Patients must have had measurable disease according to RECIST 1.1. Prior cancer therapy was allowed, including crizotinib, ceritinib, and investigational drugs and radiotherapy. Patients with controlled asymptomatic CNS involvement were permitted for inclusion. Only those with a resolution of any acute toxic effects (excluding alopecia) of any prior anticancer therapy (National Cancer Institute Common Terminology Criteria for Adverse Events or NCI CTCAE version 4.03 grade ≤ 1) were permitted.[2] There were 24 patients with ROS1 molecular characteristics of tumor of which seven patients were included in the integrated efficacy set.[21]

Intervention: In dose escalation, each cycle consisted of 28 days in repeated 4-week cycles. Dose escalation was investigated using a conventional "3+3" enrolment scheme with an accelerated titration design. Eligible patients enrolled in the dose expansion phase were grouped into molecularly-defined cohorts under a Simon's 2-stage (minmax) design determined by the type of molecular alteration harboured by the patient's tumor. Dose escalation followed an accelerated phase in which the dose was doubled in successive cohorts until one patient experienced a DLT in the first cycle or two patients experienced adverse events (AEs) at least possibly related to entrectinib that were grade ≥2 severity, but not considered to be DLTs and occurred during the first cycle, whichever came first. If these situations occurred, dose escalation followed a modified Fibonacci scheme (50, 40, or 33% increments). The starting dose was 100mg/m^2 once daily 60 minutes following a meal.[11] The recommended phase 2 dose was based on available safety, tolerability, PK and PD data from different dose levels and schedules tested. In the dose expansion stage, patients received entrectinib 600mg orally for 28 consecutive days in repeated 4-week cycles at the recommended phase 2 dose

determined during a dose escalation segment. Dose escalation treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients could continue treatment after progressive disease if determined by the investigator that treatment continued to result in a clinical benefit.[11]

Study endpoints: For dose escalation, the primary endpoint was the first cycle DLTs, MTD, and recommended phase 2 dose of entrectinib. Secondary endpoints included safety (AE type, severity, timing, ECG, and lab abnormalities), pharmacokinetics (PK), ORR, DOR, PFS, OS, biomarker assessments and pharmacodynamics (PD). For dose expansion, the primary outcome was ORR measured by RECIST version 1.1. Secondary endpoints included clinical benefit rate (CBR) according to RECIST version 1.1, progression-free survival (PFS), overall survival (OS), DOR, intracranial tumor response in patients with CNS disease according to response assessment in neuro-oncology (RANO) or RANO brain metastases (RANO-BM) by BICR assessment as applicable, safety and tolerability (characterized the same as dose escalation above), safety graded using NCI CTCAE v.4.03), biomarker assessments, PKS, and PD, as well as safety graded using NCI CTCAE version 4.03. Tumour imaging was performed at screening, at the end of Cycle 1 and approximately every eight weeks thereafter, and at the end of treatment, and as clinically indicated. In the integrated analysis, complete or partial response was confirmed with repeat imaging no less than four weeks when response criteria were first met. BICR assessment of tumour scans were conducted retrospectively, as per amendment 6.[11]

STARTRK-2

Study design: STARTRK-2 is an ongoing open-label international, multicentre, single-arm Phase II basket study in adult patients with advanced or metastatic solid tumours that involve an NTRK 1/2/3, ROS-1, or ALK gene rearrangements.[11] The objective of the study was to determine the ORR with entrectinib in each patient population basket of solid tumours.[11] STARTRK-2 is being conducted at more than 150 sites in 15 countries, not including Canada.[2] Patients are assigned to different baskets according to tumour type and gene fusion (NTRK 1/2/3, ROS1 and ALK)[11]. Depending on the patient population sub-basket, prior systemic treatment was allowed; however, prior treatment with inhibitors of NTRK, ROS1, or ALK were not allowed in patients with tumours harbouring those respective gene rearrangements except for patients with ALK or ROS-1 rearranged NSCLC with CNS-only progression who were previously treated with crizotinib.[11,25] The main baskets were NTRK 1/2/3, ROS-1, ALK, and a non-evaluable cohort who were followed over time.[11] Sub-baskets include: ALK positive - NSCLC with CNS progression post-crizotinib, ALK positive non-NSCLC solid tumours, Japan RP2D safety and tolerability sub-study, NTRK-fusion positive solid tumours, ROS-1 positive NSCLC, ROS-1 positive NSCLC CNS progression post-crizotinib, and ROS-1 positive non-NSCLC solid tumours.[24]

Population: STARTRK-2 includes adult patients ≥18 years of age, with locally advanced or metastatic solid tumours harbouring a NTRK1, NTRK2, NTRK3, ROS-1, or ALK molecular alteration. Patients must have had measurable disease assessed locally using RECIST version 1.1. Patients with CNS involvement, including leptomeningeal carcinomatosis, which is asymptomatic or previously treated and controlled, were allowed. Patients were required to have ECOG 0-2. Prior radiotherapy was allowed if at least 14 days elapsed since end of treatment (brain irradiation must have completed whole treatment 14 days prior and/or stereotactic radiosurgery at least seven days prior to entrectinib treatment). There was a total of 105 ROS-1 positive NSCLC patients of which 78 ROS-1 positive patients were included in the expanded integrated efficacy evaluable analysis set (total N = 94).[21] For the initial data cut, May 31, 2018, 37 ROS-1 positive patients were included in the integrated efficacy evaluable analysis set (total N = 53).[11]

Intervention: Entrectinib was administered at a dose of 600 mg orally as capsules on a continuous daily dosing regimen in 28-day cycles. Doses could be reduced by two dose levels (400 mg and 200 mg) to manage AEs if they were considered related to entrectinib or resumed at the initial dose if the AE was considered unrelated to entrectinib (and treatment is interrupted until the AE stabilized). Dose escalation to 800 mg once daily was allowed as per investigator's discretion after discussion with the sponsor for patients with CNS disease if they had been on treatment for at least two cycles with a best response of stable disease and without grade ≥2 AEs.[11]

Study Endpoints: The primary endpoint was ORR with a complete response defined as being sustained >4 weeks after initial response (consistent with the definition used for the integrated analysis), and CBR assessed in each patient population basket of solid tumours per gene rearrangement by prospective BICR using RECIST v.1.1.[11] Secondary outcomes included DOR, time-to-response, and CBR assessed by BICR using RECIST version 1.1. Intracranial tumor response and CNS-PFS were also secondary outcomes assessed by BICR using RANO or RANO-BM, as applicable. PFS and OS were also secondary outcomes assessed by Kaplan-Meier methodology. Quality of life and health status information was collected via self-administered instruments; European

Organization for Research and Treatment of Cancer (EORTC) quality of life instruments QLQ-C30 QLQ-LC13 (lung cancer module Core Quality of Life Questionnaire and the Lung Cancer Module.[3] Other secondary outcomes included pharmacokinetics, AEs, SAEs, laboratory assessments, vital signs, and ECGs.[11]

Statistical analysis plan: [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The primary endpoint was not met when 49 response-evaluable patients were enrolled in stage 2 and 14 responders had not been observed at 13 weeks after Cycle 1 Day 1 for the 49th response evaluable patient. Based on this, the probability of stopping enrollment was 75% at the first stage if the true response rate was 20%; whereas the probability of stopping at the first stage was 17% if the true response rate was 40%. For the ROS1-positive, ROS1 Inhibitor-Naïve NSCLC basket, the primary objective was assessed in two parts. In Part A, the statistical methods were consistent with the other baskets (i.e., with up to 62 patients enrolled, a 20% or lower response was deemed insufficient, whereas 40% or more was worthy of further examination).[24] In Part B, there was 80% power with an additional 90 patients treated at the recommended phase 2 dose was required to rule out a BICR-assessed ORR of ≤50% (null) when the true ORR is at least 65% at significance level of 0.025 (one-sided).[11,25] A pooled analysis of Part A and Part B was planned, which includes approximately 50 patients with >90% power to rule out an ORR ≤50% at a 1-sided significance level of 0.025 when the true ORR is at least 65%.

In a protocol amendment (Version 3 [Sep 9, 2016] and Version 4 [August 3, 2017]) of the STARTRK-2 trial the timing of the interim analysis was updated in support of marketing application submission for the ROS-1 positive NSCLC integrated data set.[24] Interim analyses were planned to include pooled data across phase I and phase II studies (ALKA-272-001, STARTRK-1, and STARTRK-2). Specifically, the statistical analysis plan (SAP) of the STARTRK-2 trial specified that the analyses of efficacy and safety data will occur after at least 50 ROS 1 positive NSCLC efficacy evaluable patients have been enrolled across the three phase 1 and phase 2 studies. Efficacy analyses were planned after all responding patients would have had at least 12 months of follow-up from onset of first response.[3] The May 31, 2018 data cut-off date met the requirements of this pre-planned analysis date for the integrated data set. At the time of the May 31, 2018 data cut-off date, the ROS-1 NSCLC study basket had met the primary endpoint for Part A. [redacted][28] [redacted].[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

b) Integrated Analyses

The integrated data to support efficacy are derived from a pooled subgroup of patients with ROS-1 positive metastatic NSCLC from the three trials (ALKA-372-001, STARTRK-1 and STARTRK-2) with a pre-specified final clinical cut-off date of May 31, 2018[2,28] and supplementary results provided at the October 31, 2018 and May 1, 2019 data cut-off dates.[3,11] The trials were conducted in Italy (ALKA), US, Spain, and South Korea (STARTRK-1), and 15 countries globally (STARTRK-2) - of note, none were conducted in Canada.[2] Safety data were analyzed at the final data cut-off date (May 31, 2018) and updated at the October 31, 2018 data cut-off date. Safety data were presented in two sets: 1) all patients (N = 355; May 31, 2018 and N = 504; Oct 31, 2018) (regardless of tumour type or gene rearrangement) enrolled and treated with at least one dose of entrectinib in three adults trials (ALKA-372-001, STARTRK-1 and STARTRK-2) and supplemented with few patients from one pediatric trial (STARTRK-NG) and 2) all patients (n =

134; May 31, 2018 and N = 210; October 31, 2018)[3] in the safety set that had ROS-1-postive NSCLC and received at least one dose of entrectinib. Safety data were pooled for 357 patients (2 were eventually excluded because they did not receive entrectinib, resulting in 355 patients). The safety data was not updated to align with the May 1, 2019 clinical data provided.

The integrated analysis was not pre-specified a priori in any of the individual study protocols or statistical analysis plans (ALKA, STARTRK-1, or STARTRK-2).[21] Results of integrated analyses that are conducted in this manner are generally considered exploratory in nature, as per the FDA report.[33]

The purpose of the integrated efficacy set was to maximize the number of ROS-1 positive NSCLC patients available for safety and efficacy, given the rarity of the patient population. The sponsor noted that because of the rare disease setting for ROS-1 positive NSCLC, both the FDA and EMA agreed with the approach to pool efficacy and safety data from the clinical studies (ALKA, STARTRK-1, and STARTRK-2).[3,11]

Data cut off dates for the integrated analyses set:

A summary of the data cut off dates that were provided in the integrated analyses are included in Table 10.

Table 10: Summary of Integrated Analyses

Type of data provided	Overall # patients	# patients per trial	Date of data cut off provided	Follow-up time from onset of first response*[28]
Efficacy (Primary Integrated efficacy evaluable analysis set)	N = 53	9 ALKA + 7 STARTRK-1 + 37 STARTRK-2	May 31, 2018 October 31, 2018 May 1, 2019	≥ 12 months follow-up (N = 53)
Efficacy (Extended integrated efficacy evaluable analysis set)	N = 94	9 ALKA + 7 STARTRK-1 + 78 STARTRK-2	October 31, 2018	> 12 months follow-up (N = 53) < 12 months follow-up (N = 41)
			May 1, 2019	> 12 months follow-up (N = 94)
Safety (Overall safety population; regardless of tumor type or gene rearrangement)	N = 355 N = 504	57 ALKA + 76 STARTRK-1 + 206 STARTRK-2 + 16 STARTRK-NG 60 ALKA + 83 STARTRK-1 + 332 STARTRK-2 + 29 STARTRK-NG[28]	May 31, 2018 October 31, 2018	with ≥12 and <12-months follow-up[11] Not reported
Safety (ROS-1 positive NSCLC safety population)	N = 134 N = 210	11 ALKA + 18 STARTRK-1 + 105 STARTRK-2[21] 11 ALKA + 18 STARTRK-1 + 105 STARTRK-2[28]	May 31, 2018 October 31, 2018	with ≥12 and <12-months follow-up[11] Not reported

*The definition of "onset of first response" is the duration from treatment start until the first response was observed. The onset of response is not defined as the duration until response is confirmed at a subsequent scan but can be interpreted as "unconfirmed response." The integrated efficacy evaluable analysis set comprised patients who achieved a response to treatment with entrectinib and then was followed up for ≥ 12 months. (Heath Canada Reviewer Report, page 33)

May 31, 2018 – final data cut-off

As specified in the SAP for the integrated analyses, the final analysis at the May 31, 2018 data cut-off date was pre-planned to meet the purpose of a marketing application submission after approximately 50 ROS-1 positive NSCLC patients were enrolled across the three studies (two phase 1 and one phase 2 studies). This data cut met the following criteria, as requested by the FDA and EMA: all

ROS-1 positive patients who were predicted to have at least 12 months of efficacy follow-up from the time the first response was observed or have discontinued study treatment.[28] The data cut ensured at last 12 months of follow-up in order to sufficiently characterize the durability of effect.

Safety was assessed at the May 31, 2018 data cut based on patients who received at least one dose of entrectinib.

According to the SAP, after the final May 31, 2018 data cut subsequent analyses may be performed in support of internal decision-making needs or regulatory agency requests, as appropriate. It was also stated that subsequently to the final analysis, a full safety analysis would be performed to provide five months safety follow-up data (data cut-off date of October 31, 2018) of patients that were included in the safety set of the May, 31, 2018 data cut-off date.[28]

October 31, 2018 – exploratory updated data cut

Exploratory updated efficacy data from the integrated efficacy set for the October 31, 2018 data cut-off date were prepared and submitted as part of a post-NDA submission update in the US.[3] The results for the October 31, 2018 update are included in the Health Canada Product Monograph.[3,34]

A full safety analysis was performed and pre-planned as per SAP to provide an additional five months of integrated safety follow-up data for the patients included in the original safety dataset.[28]

May 1, 2019 – exploratory updated data cut-off

According to the sponsor, updated efficacy data from the integrated efficacy set using a clinical data cut-off date of May 1, 2019 were provided in response to questions received during the review of the entrectinib (Rozlytrek) marketing application in Europe.[28] The May 1, 2019 integrated efficacy analysis was therefore not a planned analysis but was performed to support a request from a regulatory agency.

The sponsor noted that no safety data was analyzed for the May 1, 2019 data cut as there were no additional safety requests from regulatory agencies.[28]

Patient populations – Data Analysis Sets

The ROS-1 positive NSCLC Efficacy-Evaluable Population (n = 53) was the primary efficacy population for this CADTH submission. It consisted of a pooled subgroup of 53 adult patients ≥18 years of age with ROS-1 positive NSCLC who received at least one dose of entrectinib (600 mg), had at least 12 months of follow-up from the time of first response by BICR assessment, had measurable disease at baseline (per RECIST 1.1).[2] The analysis population to support efficacy for the integrated analysis is illustrated in Table 11 and Figure 2 from the three included trials.[11,21] This primary Efficacy-Evaluable Analysis Set consisted of patients enrolled up to April 30, 2017 with a clinical cut-off date of May 31, 2018. The definition of “onset of first response” is the duration from treatment start until the first response was observed. The onset of response is not defined as the duration until response is confirmed at a subsequent scan but can be interpreted as “unconfirmed response.” The integrated efficacy evaluable analysis set comprised patients who achieved a response to treatment with entrectinib and then followed up for ≥ 12 months.[21]

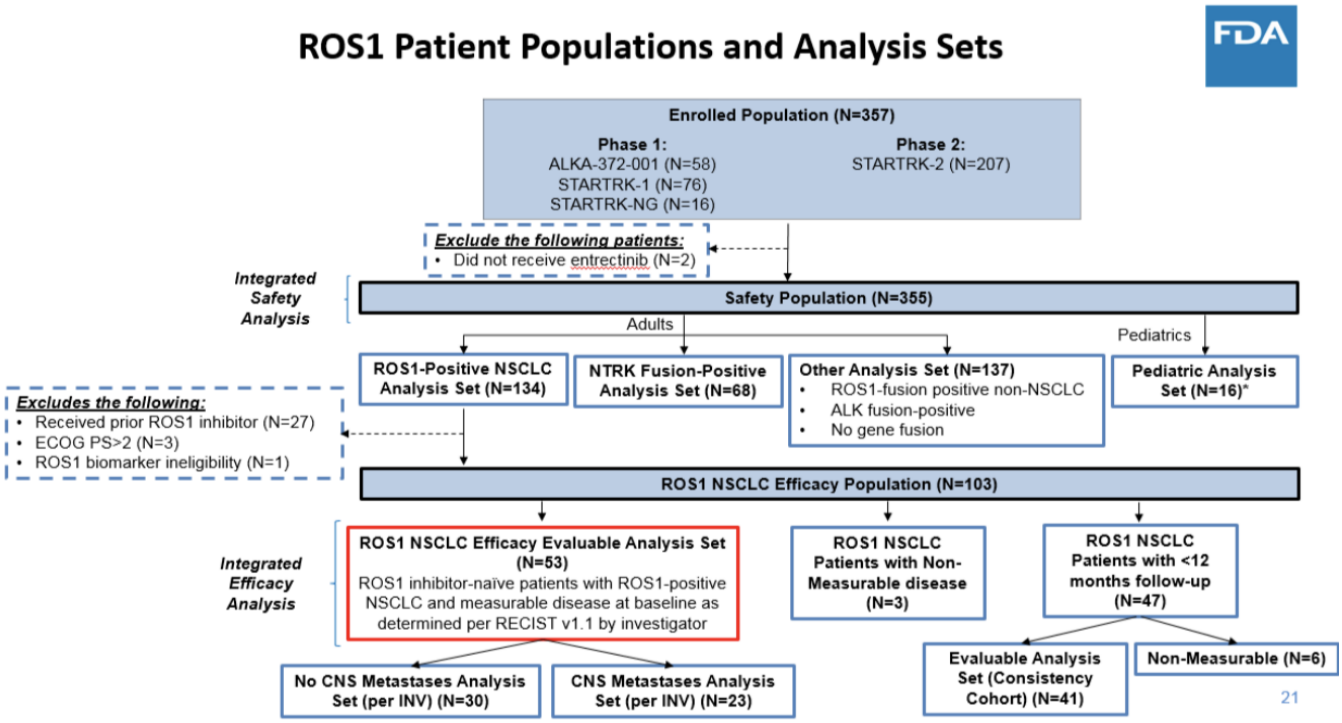
Table 11: Summary of Studies Contributing to Efficacy Evaluable Analysis Set

Study No. (Phase) [a]	Study Design	Patient Population	Entrectinib dose, Route, and Regimen	Efficacy Evaluable Patients, n
ALKA-372-001 (ALKA) (Phase I) Ongoing	First-in-human, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Patients (≥18 years old) with advanced or metastatic solid tumors with TRKA/B/C, ROS1, or ALK molecular alterations	Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m^2 once daily (fasted) 4 -days on 3-days off schedule for 3 weeks followed by a 7-day rest in a 4-week cycle [b] Schedule B: 100, 200, 400 mg/m^2/day, or 600 mg/day continuous once daily (fed) in a 4-week cycle [c] Schedule C: 400 or 800 mg/m^2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle [d]	9
RXDX-101-01 (STARTRK-1) (Phase I) Ongoing	Multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Patients (≥18 years old) with solid tumors with NTRK1/2/3, ROS1, or ALK molecular alterations	100, 200, 400 mg/m^2 once daily, 600, or 800 mg continuous once daily (fed) on 28-day (4-week) cycles	7
RXDX-101-02 (STARTRK-2) (Phase II) Ongoing	Registration-enabling, global, multicenter, open-label, basket study	Patients (≥18 years old) with advanced or metastatic solid tumors with NTRK1/2/3, ROS1, or ALK gene fusion (excluding ALK-positive NSCLC)	600 mg, orally, once daily, in 28-day (4-week) cycles	37 [e]

ALK= anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; NTRK1/2/3=Neurotrophic tyrosine receptor kinase 1/2/3; TRKA/B/C = Tropomyosin receptor kinases A/B/C.

Source: Health Canada Reviewer Report[21]

Figure 2: Patient populations



Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Additional updated analyses were performed for a pooled subgroup of 94 patients with ROS-1 positive NSCLC with measurable disease enrolled up to November 30, 2017. This subgroup (n = 94) consisted of the 53 patients in the ROS-1 NSCLC Efficacy Evaluable Analysis Set plus 41 ROS-1 NSCLC patients enrolled after April 30, 2017 and up to November 30, 2017 (complementary ROS-1 NSCLC Efficacy-Evaluable Population n = 41), who at the time of the updated data cut-off date of May 1, 2019, all had >12 months of follow-up. The 94 patients included 9 from the ALKA trial, 7 from the STARTRK-1 trial, and 78 from the STARTRK-2 trial.[28] The n = 53 and n = 94 ROS-1 NSCLC efficacy populations were also analyzed at the October 31, 2018 data cut-off date (with enrollment cut-off date of April 30, 2017),[3] at which time point 53 patients had at least 12 months follow-up from the first response and 41 patients had less than 12 months follow-up from the first response.[28]

The efficacy populations were supposed to be limited to patients who had not previously received a ROS-1 targeted treatment. The FDA reported that during the review process it was discovered that two patients in the efficacy population had received prior treatment with crizotinib which are included in the n = 94 and n = 53 data sets.[11] Overall, the n = 94 and n = 53 populations are both considered representative of the target population under review for this CADTH submission. See Table 12 below for summary of the ROS-1 NSCLC populations.

Table 12: Summary of the ROS-1 NSCLC populations

Analysis Population	Definition	Number of Patients (n)
Enrolled Population [a]	All patients enrolled into studies ALKA, STARTRK-1, and STARTRK-2	357
ROS1-positive NSCLC Analysis Set [b]	All ROS1-positive NSCLC patients who received at least one dose of entrectinib	134
ROS1 NSCLC Efficacy Population (All Patients Regardless of Follow-Up) [c]	ROS1-positive, ROS1 inhibitor-naive NSCLC patients with ROS1 biomarker eligibility and ECOG score ≤ 2	103
Primary Integrated Analysis Population:		
ROS1 NSCLC Efficacy Evaluable Analysis Set	**ROS1-positive, ROS1 inhibitor-naive NSCLC patients with measurable disease at baseline and ≥ 12 months of follow-up from onset of response**	**53**
Subpopulations:		
Patients with CNS Metastases at Baseline	Presence of CNS disease at baseline as determined by investigator	23
Patients without CNS Metastases at Baseline	Absence of CNS disease at baseline as determined by investigator	30
ROS1 NSCLC Patients with Non-Measurable Disease	ROS1-positive, ROS1 inhibitor-naive NSCLC patients with ≥ 12 months of follow-up from onset of response, and no measurable disease at baseline	3
ROS1 NSCLC Patients With ≤ 12 months of Follow-Up	ROS1-positive, ROS1 inhibitor-naive NSCLC patients with < 12 months of follow-up from onset of response; including patients with measurable (n=41) and non-measurable (n=6) disease	47
Exploratory Analysis Sets		
As Treated Analysis Set	The ROS1 NSCLC Efficacy Evaluable Analysis Set (n=53) plus patients with non-measurable disease at baseline and ≥ 12 months of follow up from onset of response (n=3)	56
ROS1 NSCLC Patients Regardless of Follow-Up Time	The ROS1 NSCLC Efficacy Evaluable Analysis Set (n=53) plus ROS1 NSCLC patients with <12 months follow-up (Evaluable Analysis Set) (n=41); includes measurable disease patients only	94

Note: Measurable disease at baseline in all populations was determined by investigator assessment as per RECIST v.1.1 criteria.

[a] The Enrolled Population (n=357) includes all enrolled patients with solid tumors containing NTRK1/2/3, ROS1 or ALK molecular alterations.

[b] The ROS1-positive NSCLC Analysis Set includes patients who were excluded from the ROS1 NSCLC Efficacy population, including those with ECOG score of >2 (n=3), those previously treated with ROS1 inhibitors (n=27), and those with ROS1 biomarker ineligibility (n=1).

[c] The ROS1 NSCLC Efficacy Population (n=103) includes patients with measurable (n=100) and non-measurable disease (n=3) as determined by investigator per RECIST v1.1 criteria.

Source: Health Canada Reviewer Report[21]

Patients had to meet the following criteria to be included in the ROS-1 NSCLC efficacy population for the integrated analysis:

- Have tumours that harbor a ROS-1 gene fusion
- Received at least one dose of entrectinib
- Have locally advanced or metastatic NSCLC
- Not treated previously with a ROS-1 inhibitor (e.g., crizotinib)
- ECOG PS of ≤2

[redacted][3]

[redacted]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Gene fusion status was determined by the following:[3]

- Presence of a ROS-1-fusion known to result in oncogenic drive activity
  - Gene fusions predicted to translate into a fusion protein with a functional kinase domain were considered positive gene fusions, versus
  - Other molecular alterations such as rearrangements, deletions, over-expression, etc. were not considered positive for a gene fusion
- Lack of co-occurrence with other strong oncodriver mutations likely to confer resistance
  - Patients with other oncogenic drivers such as EGFR were not considered evaluable for efficacy as these patients did not meet the criteria outlined above of having a sole (ROS-1 fusion) oncodriver

Patient samples that were determined to be ROS-1 positive by local testing were retested centrally by the sponsor where possible.[3]

Tumour Response Assessment: Tumour responses were assessed using computed tomography (CT) or magnetic resonance imaging (MRI) by investigator (local) assessment and by BICR and evaluated using RECIST version 1.1.[2] Screening assessments were performed four weeks prior to the first administration of entrectinib,[21] and on-treatment tumour assessments were performed at the end of every odd cycle (starting with Cycle 1), or when clinical deterioration was observed, and at End of Treatment (if not done in the previous four weeks).[21] For patients who experienced a complete response (CR) or partial response (PR), response confirmation was performed no less than four weeks from when response criteria were first met.[11] BICR assessment of tumour scans was conducted prospectively for patient enrolled in STARTRK-2, and retrospectively for patients in ALKA or STARTRK-1.[11]

Statistical Analyses

Sample Size: Assuming a true ORR (ORR-BICR) of 70%, a sample size of 50 or more patients was required to yield a 95% two-sided confidence interval (CI) with at least 17% precision that would exclude a lower limit of 50%.[2] For the integrated analysis, a response rate of 50% or higher was considered clinically meaningful.

Statistical Analysis: BICR assessed ORR and IC-ORR were presented as an efficacy summary (number and proportion of patients with confirmed CR or PR) and corresponding two-sided 95% Clopper-Pearson exact CIs.[11] To estimate time-to-event endpoints (DOR, PFS OS, IC-DOR), the Kaplan-Meier method was used with corresponding two-sided 95% CIs using Brookmeyer and Crowly (1982).[2,11] Subgroup analyses for BICR-assessed ORR by age, gender, race and region were also conducted in the primary integrated efficacy set.[11] Pre-specified sensitivity analyses included ORR and DOR as per investigator estimation, PFS by BICR and censoring for non-protocol anticancer therapy, and ORR and DOR including patients with non-measurable disease with at least 12 months of follow-up.[21]

Formal statistical significance and hypothesis testing was not performed, and thus no p-values were reported. Point estimates with 95% CIs were reported to estimate the magnitude of treatment effect. No statistical adjustments for multiplicity were made due to the rarity of the patient population and expectation of significant clinical benefit; and no statistical adjustments were made to account for subgroup effects associated with the pooling of data of the analysis for the width of the CIs.[2]

Efficacy Outcomes

Primary Outcomes: The primary efficacy outcomes were ORR, best overall response (BOR) and DOR as per BICR assessment. ORR was the proportion of patients with a confirmed CR or PR. A confirmed response was a response that persisted on repeat-imaging (CT or MRI) ≥ four weeks after initial documentation of response, and these patients were referred to as responders.[11]

DOR was calculated for responders and was measured from the date of first objective response (CR or PR) to first documentation of PD or date of death due to any cause, whichever occurred earlier. Patients were censored if they did not experience PD or death at the last tumour assessment prior to the data cut-off date.[11]

BOR was defined as the best radiologic overall response at any single time from start of treatment until disease progression based on RECIST v1.1.[11]

Secondary Outcomes: Secondary outcomes assessed by BIRC were CBR, PFS, time-to-CNS progression, OS, intracranial objective response rate (IC-ORR), intracranial duration of response (IC-DOR), and intracranial PFS (IC-PFS).[11]

CBR was defined as the proportion of patients who had met one of the following: a confirmed CR or PR; stable disease (SD) lasting at least six months since the start of entrectinib; patients who did not receive a post-baseline tumour assessment or who received at least one dose of entrectinib and discontinued for any reason prior to undergoing one post-baseline response evaluation were counted as not achieving clinical benefit.[11]

PFS was defined as number of months from first dose of entrectinib to first documentation of radiographic PD as per RECIST 1.1 or death due to any cause. Patients were censored at the date of last tumour assessment in the absence of a PD event or death prior to the time of data cut-off. For patients without a tumour assessment performed after the baseline visit, censoring occurred at the date of first dose of entrectinib.[11]

Time-to-CNS progression was defined as the time (in months) from first dose of entrectinib to first documentation of radiographic CNS PD or death due to any cause. Radiographic CNS PD was defined as an occurrence of a new CNS lesion or progression of existing CNS lesions by RECIST v. 1.1.[11]

OS was defined as the time, in months, from the first dose of entrectinib to the date of death due to any cause. Patients who were alive at the time of analysis were censored on the last known date they were alive or before the cut-off date. Additionally, patients without post-baseline information were censored on the date of the first dose of entrectinib. Patients lost to follow-up or who withdrew consent from further follow-up were censored on the last known date that they were alive or prior to the cut off-date.[11]

IC-ORR was evaluated by selecting target, non-target, or both (determined by BICR) CNS lesion(s) for each patient and evaluated by RECIST v.1.1 (patients with measurable and non-measurable CNS lesions evaluated). IC response was confirmed if the response persisted on repeat imaging ≥ four weeks after initial documentation of CNS response. Patients with CR or PR in CNS lesion(s) were referred to as IC responders.[11]

IC-DOR was calculated for IC responders, measured from the date of first IC response to first documentation of CNS PD or date of death due to any cause, whichever was earlier. Patients who did not have CNS PD and had not died within 30 days of the last dose of study treatment, IC-DOR was censored at the last tumour assessment date prior to any date of subsequent anti-cancer therapy (including surgery or radiotherapy to the brain).[11]

IC-PFS was defined as the time (in months) from first dose of entrectinib to first documentation of radiographic CNS PD or death due to any cause.

IC PD was defined as occurrence of new CNS lesion or PD in any CNS lesion as per RECIST v. 1.1. Patients without PD of IC lesion(s) or death were censored on the date of last tumour assessment prior to data cut-off.[11]

Exploratory outcome: An exploratory outcome (ORR as per investigator) was reported in the statistical analysis plan but a definition was not provided.[3]

Health-related Quality of Life: Data on patient-reported health-related quality of life (HRQoL) and health status were only collected in the STARTRK-2 trial (not ALKA or STARTRK-1 trials), as secondary outcomes, via self-administered questionnaires.[11]

The instruments used to assess the patient reported outcomes include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC Lung Cancer module (QLQ-LC13)[11] and the EuroQoL Group EQ-5D.

- QLC-C30 comprises of 30 questions assessing global health status, functioning and symptoms of both multi and single item measures[11] and was completed by all randomized patients.[24]
- QLQ-LC13 comprises of 13 questions assessing lung cancer specific symptoms and was completed for patients with lung tumours.[11,24]
- EQ-5D consists of the EQ-5D descriptive system and EQ visual analogue scale. The descriptive system consists of five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The VAS is a subjective quantitative measure of health come and measures a patient's self-rated health on a vertical visual analogue scale, between best to worst health that the patient can imagine

Patient-reported outcomes data were summarized using descriptive statistics only.[24] Each domain and item of the QLQ-C30 was linear-transformed to standardize the raw score to a range from 0-100. A clinically meaningful change from baseline was defined as an improvement or worsening of ≥10 points. A higher score on the functional scales represents a better level of functioning, and similarly, a higher score for GHS represents higher HRQoL. Conversely, a higher score on symptom scales represents higher severity of the symptom. The average score and mean change from baseline for each item in the QLQ-C30 were presented in tabular and graphical format.[11] If ≥50% of items within the multi-item subscale were missing, the score was calculated on the basis of the non-missing items. For a single-item scale, if <50% of items were missing or a single-item measure was missing, the subscale was missing.[11,24]

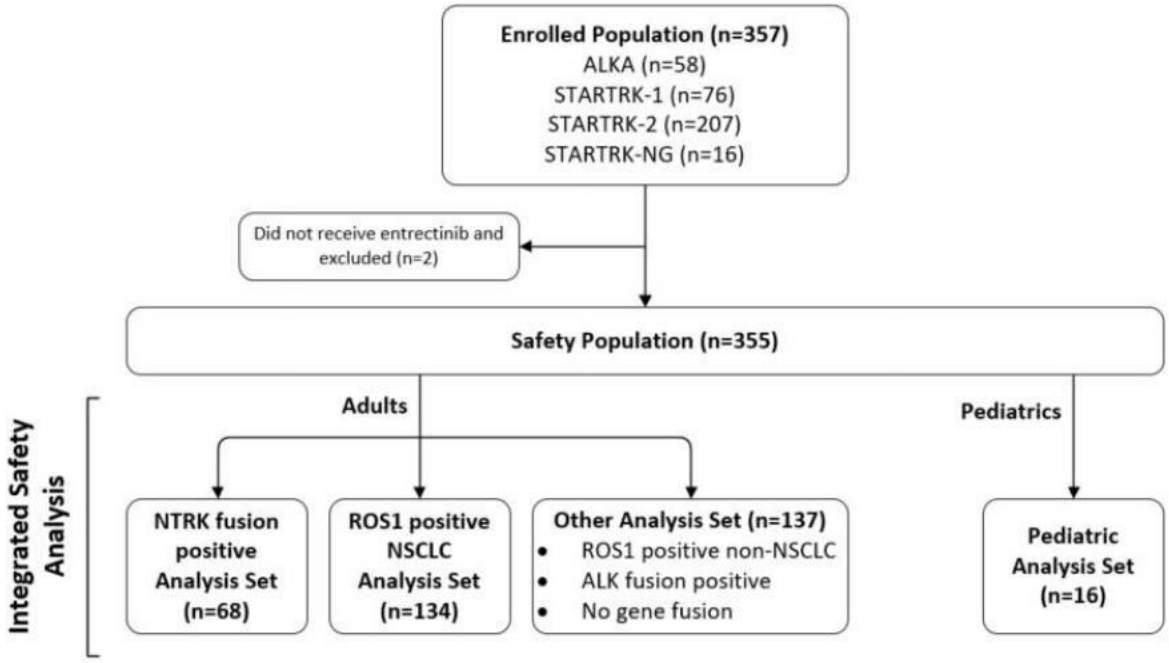
Integrated Safety Data in Adults (ROS-1 NSCLC Patient Population)

Safety Analysis Population: The safety analyses are based on the primary integrated safety population (n = 355) with a cut-off date of May 31, 2018 and updated safety analyses with a data cut-off date of October 31, 2018 (n = 504). The population of 355 patients were enrolled and treated with at least one dose of entrectinib on or before November 30, 2017. This population was comprised of patients from ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG patients. The expanded safety set (n = 504) consisted of the 355 patients in the primary integrated safety population plus 149 patients enrolled and treated with entrectinib after November 30, 2017 until October 31, 2018.[28] The sponsor also provided safety data for patients from the primary integrated safety population who had ROS-1-postive NSCLC (n = 134), which included adult patients from the three adult trials (ALKA, STARTRK-1, and STARTRK-2) which was expanded to a safety set of 210 adult patients who had ROS-1-postiive NSCLC at the October 31, 2018 data cut-off date No updated safety analyses were conducted with a data cut-off date of May 1, 2019 (i.e., to align with the efficacy updated analyses).

The patient population included in the integrated safety analysis is outlined in Figure 3. The safety population included different data sets: NTRK fusion positive, ROS-1 positive NSCLC, another analysis set (ALK fusion positive, non-NSCLC, no gene fusion), and pediatric patients. The ROS-1 positive NSCLC set (n = 134) included 27 patients who had received a prior ROS-1 inhibitor, three patients with ECOG PS of 2 or more, one patient who was deemed as having an ineligible ROS-1 biomarker status, and 47 patients who had less than 12 months of follow-up.[2] Of note, these patients were not eligible for the efficacy analysis but were eligible for the safety analysis because they had received at least one dose of entrectinib,

Safety Analyses: Summary statistics on adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), dose modifications (reductions and interruptions), discontinuations due to AEs, and deaths were reported.[2]

Figure 3: Patient Population for Integrated Safety Analysis



ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; NTRK = Neurotrophic tyrosine receptor kinase; ROS1 = ROS proto-oncogene 1 receptor tyrosine kinase.

Note: It was stated in the FDA report[11] that this figure incorrectly indicates that there were 134 patients within the ROS-1 positive NSCLC bucket, whereas the corrected number is n = 133. Information from the FDA report that is included within this CADTH CGR reports n = 133 instead of n = 134.

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

c) Populations

Eligibility criteria for selecting ROS-1 positive NSCLC patients were similar across the three trials and patient characteristics were overall balanced across the trial trials.

ROS-1 Efficacy Evaluable Analysis Set (n = 53): The ROS-1 Efficacy Evaluable Analysis Set included a total of 53 adult patients comprised of 34 (64%) female and 19 (36%) males at baseline.[2] The median age was 53 (range 27-73), with a large proportion of patients <65 years of age (n = 42; 79.2%).[11] This population included 23 patients (43.4%) that had metastatic CNS disease. The majority of patients were white (n = 31; 59%). Most patients had an ECOG PS of 1 (n = 27; 51%) or 0 (n = 20; 38%) and a minority of patients were ECOG PS of 2 (n = 6; 11%). There were 22 (42%) patients with a history of smoking; whereas just over half of patients (n = 31; 59%) did not have a smoking history.[2,3] The number of previous systemic therapies received by patients were reported [[n(%)] (0: n = 14 (26.4%), 1: n = 25 (47.2%), 2: n = 6 (11.3%), 3: n = 3 (5.7%), 4: n = 3 (5.7%), >4: n = 2 (3.8%).[2,3,11] Most patients (86.8%) had received previous anticancer therapy prior to enrollment across three studies. Chemotherapy was the most common (79.2%), followed by non-ROS-1 targeted therapy (17.0%), immunotherapy (9.4%) and hormonal therapy (1.9%).[3] Furthermore, 45.3% received previous radiotherapy and 52.8% had previous surgeries. The targeted therapies that were received by 9 patients included erlotinib (n = 5), gefitinib (n = 1), nintedanib (n = 1), and crizotinib (n = 2).[28] Detailed demographic characteristics at baseline are presented in Table 13 and Table 14.

ROS-1 NSCLC Complementary Dataset (n = 41): These patients were included in the ROS-1 Expanded Efficacy Evaluable Analysis Set (total n = 94). At the Oct 31, 2018 data cut-off date all 41 patients had less than 12 months follow up from the onset of first response. At the May 1, 2019 data cut-off date all 41 patients had at least 12 months follow-up from the time of first response.[28]

While according to the Health Canada Reviewers' report the demographic and baseline disease characteristics of these 41 patients were broadly similar with that of the 53 patients included in the ROS-1 efficacy evaluable analysis set, a few differences were noted by the CADTH Methods Team.[21] Overall, the additional 41 patients included were considered to have a poorer prognosis than the **Efficacy Evaluable Analysis Set (n = 53)**. A higher proportion of the 41 patients had Stage IV disease (80.5% vs. 61.4%, respectively) at initial diagnosis and a greater percentage had bone (41.5% vs. 37.7%) or liver metastases (24.4% vs. 15.1%) when compared to the original sample of 53 patients.[3] In addition, the complementary population had a higher proportion of Asian patients (53.7% as compared to 35.8%).[21] Fewer of the 41 patients received prior local radiation ([redacted]% vs. 45.3%) or surgery ([redacted]% vs. 52.8%) for earlier stage disease. Most of the additional 41 patients received radiation within two months prior to their first dose of entrectinib, which indicates more severe CNS disease.[3] Of the 41 patients, 61.0% had previous therapy, including chemotherapy ([redacted]), immunotherapy ([redacted]), and non-ROS-1 targeted therapy ([redacted]). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by Sponsor that it can be publicly disclosed, whichever is earlier).*

Overall ROS-1 NSCLC Efficacy Evaluable Analysis Set (n = 94): This data set consisted of 53 patients in the ROS-1 Efficacy Evaluable Analysis Set plus 41 patients from the ROS-1 NSCLC Complementary Dataset for a total of 94 patients (Table 13 and Table 14). All had measurable disease at baseline. At the May 1, 2019 data cut-off date, all patients (n = 94) were followed up for at least 12 months from their first response. The patient characteristics were as follows: median age of 53 years (range: 27 to 86), 64% were female, 49% were white, 44% were Asian, 5% were black and 2% were categorized as other; 60% never smoked; and 88% had an ECOG PS of 0 or 1. With the exception of one patient, all had metastatic disease mostly commonly in the lymph nodes (76%), lung (57%), brain (43%), bone (39%), and liver (19%). More than 75% received prior systemic therapy (76%) (e.g., any chemotherapy [71.3%], any immunotherapy [13.8%], any targeted therapy [13.8%], or any hormonal therapy [1.1%]). Further, 50% received surgery previously and 40% received radiotherapy previously.[21] More than 75% received any previous therapy, such as prior radiotherapy (40%), immunotherapy (13.8%), targeted therapy (13.8%), hormonal therapy (1.1%), chemotherapy (71%), and prior surgery (50%).[28] Overall, 33% received no prior therapy, 40% received 1 prior line of therapy and 27% received two or more lines of therapy prior to receiving entrectinib.[3]

Table 13: Key Demographic and Baseline Disease Characteristics

	Dataset		Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
	Enrolment cutoff date		**30 April 2017**	**30 April 2017 to 30 November 2017**	**30 November 2017**
			N = 53	**N = 41**	**N = 94**
Demographics	Age	median (range), years	53 (27-73)	53 (33-86)	53 (27-86)
		≥65 years, n (%)	11 (20.8%)	8 (19.5%)	19 (20.2%)
	Sex, n (%)	male	19 (35.8%)	15 (36.6%)	34 (36.2%)
		female	34 (64.2%)	26 (63.4%)	60 (63.8%)
	Race, n (%)	White	31 (58.5%)	15 (36.6%)	46 (48.9%)
		Asian	19 (35.8%)	22 (53.7%)	41 (43.6%)
		Black/African American	3 (5.7%)	2 (4.9%)	5 (5.3%)
		not reported	0	2 (4.9%)	2 (2.1%)
	ECOG PS, n (%)	0	20 (37.7%)	15 (36.6%)	35 (37.2%)
		1	27 (50.9%)	21 (51.2%)	48 (51.1%)
		2	6 (11.3%)	5 (12.2%)	11 (11.7%)
	History of smoking, n (%)		22 (41.5%)	16 (39.0%)	38 (40.4%)
Baseline Disease Characteristics	median time since diagnosis, months (range)		11.5 (0.8-169.2)	4.4 (0.7, 200.4)	7.1 (0.7-200.4)
	Disease stage at initial diagnosis, n (%)		(n = 44)	(n = 41)	(n = 85)
		I (A/B)	2 (4.5%)	3 (7.3%)	5 (5.9%)
		II (A/B	2 (4.5%)	1 (2.4%)	3 (3.5%)
		III (A/B/C)	12 (27.2%)	4 (9.8%)	16 (18.8%)
		IV	27 (61.4%)	33 (80.5%)	60 (70.6%)
		unknown	1 (2.3%)	0	1 (1.2%)
	Metastatic disease	any site, n (%)	52 (98.1%)	41 (100.0%)	93 (98.9%)
		bone, n (%)	20 (37.7%)	17 (41.5%)	37 (39.4%)
		brain, n (%)	23 (43.4%)	17 (41.5%)	40 (42.6%)
		liver, n (%)	8 (15.1%)	10 (24.4%)	18 (19.1%)
		lung, n (%)	38 (71.7%)	16 (39.0%)	54 (57.4%)
		lymph nodes, n (%)	38 (71.7%)	33 (80.5%)	71 (75.5%)
		skin, n (%)	0	1 (2.4%)	1 (1.1%)
		other, n (%)	16 (30.2%)	15 (36.6%)	31 (33.0%)

	Dataset		Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
	Enrolment cutoff date		**30 April 2017**	**30 April 2017 to 30 November 2017**	**30 November 2017**
			N = 53	**N = 41**	**N = 94**
Previous Cancer Treatment	No of prior systemic therapies[a], n (%)	0	14 (26.4%)[c]	17 (41.5%)	31 (33.0%)
		1	25 (47.2%)	13 (31.7%)	38 (40.4%)
		2	6 (11.3%)	7 (17.1%)	13 (13.8%)
		3	3 (5.7%)	1 (2.4%)	4 (4.3%)
		4	3 (5.7%)	0	3 (3.2%)
		>4	2 (3.8%)	3 (7.3%)	5 (5.3%)
	Previous therapy, n (%)	any systemic therapy[b]	46 (86.8%)	25 (61.0%)	71 (75.5%)
		surgery	28 (52.8%)	19 (46.3%)	47 (50.0%)
		radiotherapy	24 (45.3%)	14 (34.1%)	38 (40.4%)
	Baseline CNS lesions by INV		**n=23**	**n=17**	**n=40**
	Previous radiotherapy to brain, n (%)		14 (60.9%)	6 (35.3%)	20 (50.0%)

Source: Submission materials[3]

Table 14: Other Baseline Patient and Disease Characteristics

	Primary Analysis Set (n=51)	Measurable Disease Set* (n=94)	Efficacy Analysis Set* (n=103)
ECOG Performance Status			
0	19 (37.2%)	35 (37.2%)	38 (36.9%)
1	26 (51.0%)	48 (51.1%)	53 (51.5%)
2	6 (11.8%)	11 (11.7%)	12 (11.7%)
Smoking Status			
Never Smoker	29 (56.9%)	38 (40.4%)	60 (58.3%)
Former/Current Smoker	22 (43.1%)	56 (59.6%)	43 (41.8%)
Number of Prior Systemic Therapies**			
0	7 (13.7%)	23 (24.5%)	38 (36.9%)
1 or 2	20 (39.2%)	29 (30.9%)	53 (51.5%)
≥3	24 (47.1%)	42 (44.7%)	12 (11.7%)
Extent of Disease at Start of Treatment			
Localized	1 (2.0%)	1 (1.1%)	1 (1.0%)
Local Advanced	2 (03.9%)	2 (2.1%)	6 (5.8%)
Metastatic Disease	48 (94.1%)	91 (96.8%)	96 (93.2%)
Histology			
Adenocarcinoma	48 (94.1%)	91 (96.7%)	100 (97.1%)
Others	3 (5.9%)	3 (3.3%)	3 (2.9%.)
CNS Measurable Disease at Baseline (BICR)			
No	7 (13.7%)	19 (20.2%)	19 (18.5%)
Yes	12 (23.5%)	16 (17.0%)	17 (16.5%)
CNS Metastases Baseline (BICR)			
No	32 (62.8%)	59 (62.8%)	67 (65.1%)
Yes	19 (37.2%)	35 (37.2%)	36 (35.0%)
CNS Metastases Baseline (INV)			
No	29 (56.9%)	54 (57.5%)	60 (58.3%)
Yes	22 (43.1%)	40 (42.5%)	43 (41.7%)
Any Prior Radiotherapy of the Brain***			
No	37 (72.6%)	73 (77.7%)	78 (75.7%)
Yes	14 (27.4%)	21 (22.3%)	25 (24.3%)

**includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*

***33% of the 51 patients in Primary Analysis Set had no prior line of systemic therapy for metastatic disease; 67% of the 51 patients in Primary Analysis Set received prior platinum-based chemotherapy for metastatic or recurrent disease; one patient started treatment with entrectinib within 6 months of completion of platinum-based neoadjuvant/adjuvant chemotherapy*

****one patient who had prior radiotherapy of the brain with missing data for time from end of prior radiotherapy to first dose of entrectinib*

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Safety Analysis Population: Sex, ethnicity, and ECOG PS of the ROS-1 Integrated Efficacy Evaluable Analysis Set (n = 53) was largely consistent with the overall Safety Analysis Population (n = 355) and ROS-1 Safety Analysis set (n = 133; note the FDA report confirmed that there were 133 patients in this data set and the 134 patients was an error).[11] The patient characteristics of the Safety Analysis Population (n = 355) were as follows: median age of 55 years (range: 4 to 86), 55% were female, 66% were White, 23% were Asian, 4.5% were Black or African American, and 5% did not report their race. In addition, 91% had an ECOG PS of 0 or 1. An overview of the population is available in Table 15. In addition, most adult patients had no history of smoking (57.2%,183/320) with the remaining 42.8% (137/320) being current or previous smokers.[3]

Table 15: Demographic characteristics of the Safety Analysis Population, n = 355

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult (non *NTRK*, *ROS1*) (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Sex					
Male (%)	46	40	49	62	45
Female (%)	54	60	51	38	55
Median Age (yrs)	58	53	55	10	55
Range	21-83	15-86	15-80	4-20	4-86
Age (yrs)					
<65 (%)	63	76	76	100	75
≥65 (%)	37	24	24	0	25
Ethnicity					
Hispanic or Latino (%)	6	2	3	6	3
Not Hispanic or Latino	86	92	88	81	89
Not stated (%)	6	2.5	1	6	3
Unknown (%)	1.5	4	8	6	5
Race					
White (%)	77	53	72	81	66
Asian (%)	13	38	16	0	23
Black or AA (%)	1.5	5	4	19	4.5
Not reported (%)	9	3	4	0	4.5
ECOG PS (%)					
0	38	39	45	0	41
1	49	50	51	0	50
2	10	8	4	0	7
3	3	0.7	0	0	0.9
4	0	0.7	0	0	0.3

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Note: It was stated in the FDA report[11] that it was incorrectly reported that there were 134 patients within the ROS-1 positive NSCLC bucket, whereas the corrected number is n = 133. Information from the FDA report that is included within this CADTH CGR reports n = 133 instead of n = 134.

Data on an expanded data set were provided with a total sample of 504 patients with an enrollment date of October 31st, 2018; 60 patients were from ALKA, 83 patients from STARTRK-1, 332 patients from STARTRK-2, and 29 from STARTRK-NG. The characteristics for the entire sample of 504 patients were as follows: mean age of 52 years, 55% were female, 62% were White, 26% were Asian, and 12% were categorized as other races; 59% did not have a history of smoking, and 91% had an ECOG PS of 0 or 1. Of these, 210 patients were included in an additional safety analysis set that included ROS-1 positive adults only, including 11 patients from ALKA, 20 patients from STARTRK-1, and 179 patients from STARTRK-2. A summary of the patient characteristics for the overall sample of 504 patients can be found in Table 16.[28]

Table 16: Demographic characteristics of the Expanded Safety Analysis Population, n = 504

Demographic and Baseline Disease Characteristics Safety Evaluable Patients

	Safety Evaluable Patients (n=504)
Sex male	 227 (45.0%)
Age (years) n mean	 504 51.7
Race n Asian White Other	 503 131 (26.0%) 310 (61.6%) 62 (12.4%)
ECOG	
n 0 1 2 3 4	474 199 (42.0%) 233 (49.2%) 38 (8.0%) 3 (0.6%) 1 (0.2%)
History of Smoking n No Yes Current Former	 452 266 (58.8%) 186 (41.2%) 29 (15.6%) 157 (84.4%)

Source: Sponsor checkpoint follow-up response[28]

d) Interventions

ROS-1 Efficacy Evaluable Analysis Set

Treatment Dosing: Patients included in the integrated analysis received treatment until any of the following: documented radiographic progression, withdrawal of consent, or unacceptable toxicity.[2] Patients received treatment in 4-week cycles, which could be continuous or intermittent for the ALKA trial (depending on what schedule patients in the ALKA trial were on (Schedule A, B, or C), they

could receive intermittent or continuous dosing) or continuous only in the STARTRK-1 and STARTRK-2 trials[25] (see Table 8 for dosing schedules of individual trials)

ROS-1 Primary Efficacy Evaluable

Analysis Set (n = 53) (May 31, 2018 data cut-off date): All 53 patients received at least one dose of entrectinib at or above the recommended phase 2 dose of 600 mg once daily. Most patients (n = 47) received the recommended dose of entrectinib at 600 mg once daily. Six patients received a dose above or below 600 mg once daily. One patient started on 400 mg and then 600 mg on day 2 and 600 mg thereafter. Another patient received entrectinib at 800 mg on a 4 days on and 3 days off schedule. Four patients were administered entrectinib at a higher dose (650-2000mg at varying schedules).[3,28] The median treatment duration with entrectinib was 14.62 months in the ROS-1 Efficacy Evaluable Set for the May 31, 2018 cut-off or a median of 17 cycles.[3]

ROS-1 Primary Efficacy Evaluable Analysis Set (n = 53, n = 94) (Oct 31, 2018 data cut-off date)

There were nine patients from ALKA, seven from STARTRK-1, and 78 from STARTRK-2 who contributed to the subgroup of n = 94 ROS-1 NSCLC Efficacy Evaluable patients with measurable disease enrolled up to November 30, 2017.[28] The median duration of treatment was 18.0 months (range 0.1, 42.1) for the n = 53 data set and 13.7 months (range 0.1, 42) for the n = 94 data set.[28] Among 94 patients, 88 (94%) patients received the recommended entrectinib dose of 600 mg daily.[21]

ROS-1 NSCLC Overall Efficacy Evaluable Analysis Set (n = 94) (May 1, 2019 data cut-off date)

For the May 1, 2019 cut-off, the median duration of treatment with entrectinib was 15.8 months (range: 0.1-43.2 months) or a median of 19.5 cycles.[3]

Treatment beyond progression: For the May 31, 2018 data cut off, 28 of the 53 patients received entrectinib (at least one dose) after progression of disease according to RECIST version 1.1 as per investigator assessment. This was allowed in the protocol, if the investigator deemed the patient was still experiencing a clinical benefit. No definition of clinical benefit was provided. For 11 patients, the last dose of entrectinib was administered within one month of the first investigator determined disease progression as per RECIST version 1.1; of note, this could have been due to a delay in the interpretation or analysis of the radiological scans. The remaining 17 patients continued entrectinib beyond 1 month after the first investigator-determined progressive disease date. For most of the 17 patients, the sponsor received requests from investigators to continue the medication, as it was deemed that it was of clinical benefit to the patient. The sponsor encouraged the investigators to continue with the assessment schedule for documentation and clinical assessment purposes.[28]

For the May 1, 2019 data cut-off, 50 of the 94 (53%) patients in the ROS-1 NSCLC Efficacy Evaluable population received at least one dose of entrectinib after the date that the investigator determined progression of disease to have occurred. In 18 of the 50 cases for NSCLC ROS-1, the last dose of entrectinib was administered within 1 month of the first investigator-determined progression of disease date. In the remaining 32 cases for ROS-1 NSCLC, treatment with entrectinib continued beyond one month after the investigator determined the progression of disease date.[28]

Concomitant Medications: The following medications were permitted across the trials:[25]

- ALKA, STARTRK-1 and STARTRK-2: antiemetics (with caution), antidiarrheal drugs, antacids (discontinue before treatment with entrectinib, H2 receptor blockers preferred administered at least three to four hours after entrectinib), palliative radiotherapy to specific sites (if medically necessary), seizure prophylaxis and non-enzyme-inducing anti-epileptic drugs (non-EIAEDs) for controlled asymptomatic CNS involvement (enzyme-inducing anti-epileptic drugs prohibited), and prophylactic use of granulocyte colony-stimulating factor (G-CSF) or erythropoietin according to the American Society of Clinical Oncology guidelines for severe neutropenia or anemia (note: not permitted in Cycle 1 for ALKA and STARTRK-1 only).[25] Any therapy for patient wellbeing was permitted unless it increased QTc interval or caused arrythmia.
- STARTRK-1 and STARTRK-2: corticosteroids were allowed for pneumonia and moderate to strong inhibitors and inducers of cytochrome P450 CYP3A were to be used with caution, as well as cytochrome P450 substrates. The following medications were to be used with caution: antiarrhythmics, antipsychotics, antibiotics, antidepressants, antiepileptics, (STARTRK-1 only) and antiemetics (both STARTRK-1 and STARTRK-2). Furthermore, it was recommended to avoid herbal medicines or citrus fruit/juices.[25]

- In STARTRK-2: concomitant surgery was permitted, as well as bone-sparing agents for bone metastases or treating osteoporosis/osteopenia (e.g., bisphosphonates) and the inactivated influenza vaccine for the seasonal flu.

Safety Analysis Population

Treatment Dosing: The safety data in the overall Safety Analysis Population (n = 355) at the May 31, 2018 data cut-off date reflects the safety of entrectinib across multiple dose levels, where most adult patients (76%) received the recommended phase 2 dose (RP2D) of 600 mg as the starting dose. The median duration of entrectinib treatment was 5.5 months (range: 1 day to 42 months) across the overall Safety Analysis Population with a median of seven cycles (range 1 to 92). The mean cumulative dose was 123,405.93 mg; furthermore, 61.4% of patients received entrectinib for more than three months, 48.5% received entrectinib for more than six months, 33.2% received entrectinib for more than nine months, and 23.7% received entrectinib for more than 12 months. The summary of entrectinib exposure in the overall Safety Analysis Population is presented in Table 17. Of note, the ROS-1 Adult Safety Population (n = 133) had a longer median duration (8.3 months; 95% CI: 0.1,42.1) compared to the overall Safety Analysis Population (5.5 months; 95% CI: 0.0, 42.1), as most of these patients were enrolled from STARTRK-2, where patients were selected based on the presence of certain biomarkers (including ROS-1 fusions). Namely, patients with ROS-1 positive NSCLC were predicted to respond to entrectinib.[11]

Table 17: Summary of entrectinib exposure in the Safety Analysis Population, n = 355

Parameter	*NTRK* Adult (n=68)	*ROS1* NSCLC Adult (n=133)	Other Adult (n=137)	Pediatric (n=17)	All (n=355)
Median treatment duration (Months)	7.9 (0.1, 24.7)	8.3 (0.1, 42.1)	2.0 (0.0, 37.0)	1.9 (0.2,12.7)	5.5 (0.0, 42.1)
Median no. of cycles	9.5 (1.0, 49.0)	10.0 (1.0, 92.0)	3.0 (1.0, 70.0)	4.0 (1.0, 16.0)	7.0 (1.0, 92.0)
Median no. of missed doses	1.0 (0.0, 34.0)	1.0 (0.0, 24.0)	0.0 (0.0, 17.0)	2.0 (0.0, 37.0)	1.0 (0.0, 37.0)
Median dose intensity, %*	94.1 (40.5, 105.3)	96.5 (29.8, 133.3)	98.6 (12.6, 388.3)	96.3 (32.6, 115.1)	96.9 (12.6, 388.3)

*Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

Source: Reviewer generated table based on: Module 5.3.5.3 Analysis dataset_AEX. Derivations: BASKGRP3; TRTSDTM: Date/time of first exposure to treatment; TRTEDTM: Date/time of last exposure to treatment; TRTDURM: Duration of exposure (months)

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

In the expanded integrated safety analysis including 504 patients at the October 31, 2018 data cut-off date, the median treatment duration in months was 5.5 months (range: 0.0, 42.1) and median number of cycles was 7.0 (range: 1.0, 92.0). The median number of missed doses was 1.0 (range: 0.0, 50.0), mean cumulative dose was 121,355 mg, and median dose intensity was 96.4%. Details are provided in Table 18. In the expanded ROS-1 adult safety set (n = 210), the median treatment duration in months was 7.4 months (range: 0.0, 42.1), and median number of cycles was 10.0 (range: 1.0, 92.0). The median number of missed doses was 1.0 (range: 0.0, 25.0), the mean cumulative dose was 121,355 mg, and the median dose intensity was 94.9%. Details are provided in Table 19.

Table 18: Summary of entrectinib exposure in the Safety Analysis Population, n = 504

	All patients (n=504)
Median treatment duration, months (range)[a]	5.5[c] (0.0, 42.1)
Median no. of cycles (range)	7.0 (1.0, 92.0)
Median no. of missed doses (range)	1.0 (0.0, 50.0)
Mean cumulative dose, mg (SD)	121,355[c] (137,269)
Median dose intensity, % (range)[b]	96.4[c] (12.6, 388.3)

a Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

b Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

c n=501. Three patients in the GO40782 (STARTRK-2) study had only one dose with an unknown end date, hence the duration of exposure was unknown.

Source: Sponsor checkpoint follow-up response[28]

Table 19: Summary of Extent of Exposure to Entrectinib in the ROS-1-NSCLC Adult Patients, n = 210

	ROS1 NSCLC Adult Patients (n=210)
Median treatment duration, months (range)[a]	7.4 (0.0, 42.1)

Median no. of cycles (range)	10.0 (1.0, 92.0)
Median no. of missed doses (range)	1.0 (0.0, 25.0)
Mean cumulative dose, mg (SD)	153,029 (160, 342)
Median dose intensity, % (range)[b]	94.9 (13.6, 133.3)

a Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

b Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

Source: Sponsor's checkpoint follow-up response[28]

e) Patient Disposition

ROS-1 Efficacy Evaluable Analysis Set (n = 53) (May 31, 2018 data cut)

As of the data cut-off date (May 31, 2018), 51% of patients were still receiving active treatment, while 41% discontinued treatment. Eight patients (36%) had died among the 41% who discontinued the study. Of the other 30 patients who discontinued treatment, the most common reason was disease progression (77%).[11] The patient disposition as per the May 31 2018 cut-off is presented in Table 20. Of note, in the FDA report, two patients of the 53 were excluded from this table , as they received treatment with crizotinib.

Table 20: Summary of patient disposition in the ROS-1 Efficacy Evaluable Analysis Population, n = 51** - May 31, 2018 data cut

Populations	Primary Analysis Set (n=51)	Measurable Disease Set* (n=94)	Efficacy Analysis Set* (n=103)
Study Status			
Completed	4 (7.8%)	4 (4.3%)	5 (4.9%)
Ongoing	26 (51.0%)	58 (61.7%)	65 (58.3%)
Discontinued	21 (41.2%)	32 (34.0%)	33 (36.9%)
Reasons for Discontinued Study	n=22	n=32	n=33
Death	8 (36.4%)	17 (53.1%)	17 (51.5%)
Informed Consent Withdrawn	6 (27.3%)	7 (21.9%)	7 (21.2%)
Withdrawal by Subject	2 (9.0%)	2 (6.3%)	2 (6.1%)
Others	6 (27.3%)	6 (18.8%)	7 (21.2%)
Reasons for Discontinued Treatment	n=30	n=48	n=51
Progressive Disease	23 (76.7%)	35 (72.9%)	37 (72.6%)
Adverse Event	5 (16.7%)	9 (18.8%)	10 (19.6%)
Informed Consent Withdrawn	2 (6.7%)	3 (6.3%)	3 (5.9%)

** Includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

ROS-1 Efficacy Evaluable Analysis Set (n = 53) (October 31, 2018 data cut)

For the October 31, 2018 cut-off, 22 (41.5%) patients of the 53 total patients were ongoing in the three studies (ALKA, STARTRK-1, and STARTRK-2), four (7.5%) completed the study (all from the ALKA trial), and 12 (44.4%) died.[21] Patients discontinued a study for the following reasons (n, %): death (12, 44.4%), withdrawal due to informed consent (7, 25.9%), withdrawal by subject (2, 7.4%), and other reasons not specified (6, 22%). Thirty-six (67.9%) patients discontinued entrectinib overall for the following reasons (n, %): disease progression (29, 80.6%), AEs (5, 13.9%), and withdrawal of consent (2, 5.6%).[28]

ROS-1 NSCLC Efficacy Evaluable Analysis Set (n = 94) – Data cut May 1, 2019

At the May 1, 2019 cut-off, 46 patients (48.9%) were still ongoing in the study and four patients (all from the ALKA trial) were deemed as having follow-up completed as per protocol. Overall, 44 patients (46.8%) out of the 94 patients in the ROS-1 Efficacy Data Set discontinued the study with the most common reasons being due to death (24 patients, 54.5%), withdrawal of consent (22.7%), progressive disease (2.3%), subject withdrawal (4.5%), and for other reasons not specified (15.9%). Sixty-five patients (69.1%) discontinued treatment overall; reasons (n,%) for treatment discontinuation included: disease progression (51, 78.5%), AEs (10, 15.4%), and other reasons [informed consent withdrawal (4.6%) and “other” (1.5%)].[3,28]

Protocol Deviations: Protocol deviations occurred in all three trials (ALKA, STARTRK-1, STARTRK-2). A quarter of patients (n = 88; 24.8%) experienced at least one major/important protocol deviation, and a total of 117 major protocol deviations occurred. The most common protocol violations included an eligibility criteria violation (n = 22; 6.2%), followed by informed consent issues (n = 16; 4.5%), and medication errors (n = 13; 3.7%).[11] [redacted].[28]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Major protocol deviations were reported for each trial separately:

ALKA:[11]

- Eligibility criteria was not met (39%)
- Errors in treatment administration (16%)
- Radiologic assessment (11%)
- Concomitant treatments that were not allowed (2%)
- Informed consent document not signed (2%)
- Issues with documentation (2%)

STARTRK-1:[11]

Major protocol deviations were defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or the patients' rights, safety, or wellbeing. Overall, 15 (19.7%) patients had deviations that met the definition of major deviation. These deviations included receiving concurrent medications (e.g., Phenergan, Levaquin, ciprofloxacin), failure to collect a pregnancy test, crizotinib or radiation therapy washout period being shorter than protocol specification, or incorrect dose (400 mg instead of 800mg).

- Study conduct/procedures
  - Study restrictions/Withdrawal Criteria (5; 6.6%)
  - Inclusion/Exclusion Criteria (4; 5.3%)

STARTRK-2:[11]

Overall, 48 (23.3%) patients had a major protocol deviation. These were related to:

- Informed consent (15; 7.3%)
- Eligibility and entry deviation (10; 4.9%)
- IP compliance (10; 4.9%)

Protocol violations for the safety analysis (N = 355, including pediatric patients), are outlined in Table 21. Although 117 important protocol deviations occurred in 88 patients, the FDA report indicated that these likely did not materially alter the assessment of safety or effects on ORR and DOR for entrectinib in patients with ROS-1-positive NSCLC.[11]

Table 21: Summary of major/important protocol violations in the Safety Analysis Population, n =355

Protocol Violation	Overall Safety Analysis Population N=355 n (%)
Patients with major protocol violation (%)	88 (24.8)
Total number of major protocol violations	117
Issues with informed consent	16 (4.5)
Protocol procedures/visits not performed/missing	4 (1.1)
Inclusion/Exclusion criteria violated	22 (6.2)
Incorrect response assessment	6 (1.7)
Out of window visits/procedure	0
Medication errors	13 (3.7)
Other[1]	2 (0.6)

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Subsequent treatment: In the Primary ROS-1 NSCLC Efficacy-Evaluable Analysis Set (n = 53) at the May 31, 2018 clinical data cut-off date, 15 (28.3%) patients were treated with anti-cancer treatments before progression by BIRC RECIST assessment. Twelve (22.6%) patients received antineoplastic agents including (in order of frequency): pemetrexed, platins, nivolumab, and docetaxel and paclitaxel. After disease progression, as assessed by the BICR, one patient (1.9%) received anti-cancer treatment with an antineoplastic agent.28

In the Overall ROS-1 NSCLC Efficacy-Evaluable Analysis Set (n = 94) at the May 1, 2019 data cut-off date, 31 (33.0%) patients were treated with anti-cancer treatments before progression by BIRC RECIST assessment. Twenty-four (24.5%) patients received antineoplastic agents including (in order of frequency): pemetrexed, platins, nivolumab, gemcitabine, and pemetrexed disodium. After disease progression, as assessed by the BICR, 14 patients (14.9%) received anti-cancer treatment. Thirteen (13.8%) patients received antineoplastic agents including (in order of frequency): crizotinib, protein kinase inhibitors, pemetrexed, and carboplatin.[28]

f) Limitations/Sources of Bias

Several limitations are apparent in the three individual trials and integrated analysis, as follows:

- Biases in single-arm trials: All trials were single-arm and unblinded. The non-randomized and non-comparative design of the trials complicates the interpretation of the efficacy and safety data for entrectinib because all patients received the same treatment. The lack of comparison with an active comparator or standard of care/placebo precludes the ability to assess the relative therapeutic benefit or safety of entrectinib against a relevant comparator.
- Limited interpretation of time-to-event endpoints: Interpretation of time-to-event endpoints such as OS or PFS is limited in single-arm studies. As noted in the FDA Guidance for Industry[1], because of variability in the natural history of many forms of cancer, a randomized trial is required to evaluate time-to-event endpoints.
- Limited interpretation of safety data: Due to the non-comparative nature of the analyses it is not possible to clearly determine if symptoms are related to the underlying malignancy or to entrectinib-related adverse events.
- No formal statistical testing: Formal statistical significance and hypothesis testing was not performed, and thus no p-values were reported. Point estimates with 95% CIs were reported to estimate the magnitude of treatment effect. No statistical adjustments for multiplicity were made due to the rarity of the patient population and expectation of significant clinical benefit; and no statistical adjustments were made to account for subgroup effects associated with the pooling of data for integrated analysis.
- Ongoing nature of the studies: ALKA and STARTRK-1 are completed; however, STARTRK-2 is ongoing with an estimated completion date of [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by Sponsor that it can be*

publicly disclosed, whichever is earlier). As such, the results are from a pre-specified interim analysis and the results might not be reflective of the final results after recruitment and follow-up is complete. In the integrated efficacy set the median follow-up for OS was 20.9 months, therefore long-term survival beyond 1.5 years cannot be estimated in this trial. Furthermore, OS data in the integrated efficacy set were immature (i.e., median OS not reached) at the latest data cut-off date (May 1, 2019) .[28]

- Use of efficacy results from phase 1 trials: Two phase 1 trials were included in the integrated analysis. The purpose of a phase 1 study is to examine safety and not efficacy although efficacy outcomes were included, they are specified as being exploratory in nature. No firm conclusions can be made on efficacy using these data, particularly in the absence of inferential statistical testing.
- Missing information on CNS status: Of the 51 patients included in the Primary ROS-1 Efficacy Evaluable dataset (n = 53), 62.7% had a status of "missing" for CNS measurable disease at baseline assessment as per BICR. This suggests that the CNS sub-group analyses should be interpreted with caution.[11]
- Pooling results in the integrated analysis: The results from 3 separate studies were pooled and although there are some similarities across the studies, there were several differences noted by the CADTH Methods team. There were different phases of the trials; ALKA and STARTRK-1 were single arm phase I trials, whereas STARTRK-2 was a phase II single arm, basket trial. However, similar dosing was used across the trials. Different primary outcome measures were pre-specified, and differences in outcome definitions occurred between the studies. For example, BICR was conducted retrospectively for ALKA and STARTRK-1 trials and prospectively for STARTRK-2. The approach to combine these trials without any adjustments for heterogeneity may introduce biases into the results. The sponsor noted that because of the rare disease setting for ROS-1 positive NSCLC, both the FDA and EMA agreed with the approach to pool efficacy and safety data from the clinical studies (ALKA, STARTRK-1, and STARTRK-2).

  The integrated analysis was not pre-specified a priori in any of the individual study protocols or statistical analysis plans (ALKA, STARTRK-1, or STARTRK-2).[21] Results of integrated analyses that are conducted in this manner are generally considered exploratory in nature, as per the FDA report.[33]
- Limited sample size: Despite pooling to maximize the number of patients to inform the efficacy of entrectinib, there were a limited number of patients included in the efficacy data set (n = 53, n = 94). As such, it is unclear whether the basket trial and integrated analysis is sufficiently generalizable to Canadian clinical practice and whether the same magnitude of treatment effect would be observed in a larger study population. Furthermore, sample sizes for the subgroups are smaller and associated with wide CIs. The lack of statistical testing and adjustments for multiple comparisons adds to the uncertainty associated with the results. Therefore, the results of any subgroup analyses should be interpreted with caution.
- Health related quality of life outcomes: No statistical analyses were planned only descriptive and summary statistics. The number of patients for whom PRO data were available steadily declined over the course of the study which limits the interpretation of the results especially at later cycles (Cycle 23; only 18 patients out of 78 patients provided patient-reported outcomes data). Additionally, the trial was non-randomized and the impact of entrectinib in relation to other therapies is unknown. As such, the health-related quality of life results need to be interpreted with caution.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

May 31, 2018 data cut-off date; ROS-1 Efficacy Evaluable Analysis Set, n = 53: For the May 31, 2018 cut-off, the median duration of follow-up from the time of first response was 16.6 months (95% CI: 13.8-17.9) and the median survival follow-up was 15.5 months (95% CI: 14.8-19.0).

A summary of ORR, BOR, DOR as per BICR for the efficacy analyses is shown in Table 22 and the Kaplan Meier curves are presented in Figure 4. Forty-one of the 53 patients experienced a confirmed response at the data cut-off (72%). The ORR by BICR was 77% (95% CI: 64-88). These results were consistent with the investigator assessment of the ORR (76.5%, 95% CI: 62.5-87.2%).[11]

Sub-group analysis was conducted in the integrated analysis according to CNS status. At baseline, 23 patients were classified as having measurable CNS disease and were compared with 30 patients classified as having no CNS disease in a sub-group analysis for the integrated analyses. The efficacy of entrectinib in patients with and without baseline CNS metastases is highlighted in Table 22. The BICR-assessed ORR in patients without baseline CNS metastatic disease was 80% (95% CI: 61%-92%) (24 patients) and it was 74% (95% CI: 52%-90%) for patients with baseline CNS disease (17 patients).[2]

For the BOR, a total of 3 (6%) of the 53 patients achieved a complete response, 38 (72%) had a partial response, and one (2%) had stable disease as their best objective response to entrectinib. Others include four (8%) with progressive disease, three (6%) with

non-complete response/non-progressive response and four (8%) with missing data or unevaluable data. For patients with CNS disease as determined by investigator, 17 (74%) had a partial response, four (17%) had progressive disease, and two (8%) had missing or unevaluable data; whereas no patients experienced a complete response, stable disease, or a non-complete response/non-progressive disease. For patients without baseline CNS disease, three patients (10%) experienced a complete response, 21 patients (70%) had a partial response, one patient (3%) had stable disease, three patients (10%) had non-complete response or non-progressive disease and two patients (7%) had missing or unevaluable data.[2]

The BICR DOR among responders was a median of 24.6 months (95% CI: 11.4, 34.8) overall (25th percentile: 9.1, 75th percentile: 34.8; range: 1.8 to 34.8).[2,3] For the DOR as confirmed by the investigator, the results were slightly shorter (median 16.8 months, 95% CI: 12.7-21.4).[11] Similar to the ORR, the DOR was longer for patients with no baseline CNS disease at 24.6 months (95% CI: 11.4-34.8) compared to 12.6 months (95% CI: 6.5, not estimable) for patients with baseline CNS disease.[2] The number of patients experiencing DOR among the 40 responders was 30 (75%) for ≥6 months, 27 (67.5%) for ≥9 months, 17 (42.5%) for ≥12 months, and seven (17.5%) for ≥18 months.[11]

Eleven of the 20 patients with CNS disease at baseline experienced an intracranial response (complete response in 20%, 4/20 and partial in 35%, 7/20), as indicated in Table 22. The Intracranial ORR was 55% (95% CI: 32-77%). The intracranial DOR was 12.9 months (95% CI: 4.6, NE).[2] Of note, 44% (4/9) patients with responses had received radiation to the CNS within two months prior to receiving their first dose of entrectinib.[11]

PFS is presented in Table 22. There were 25 patients (47.2%) who experienced a PFS event at the time of data cut-off and the median PFS was 19.0 months (95% CI: 12.2-36.6; 25th percentile: 7.7, 75th percentile: 36.6; range: 0 to 36.6).[2,3] Fourteen patients without baseline CNS disease experienced a PFS event and the PFS was a median of 26.3 months (95% CI: 15.7, 36.6). Eleven patients with baseline CNS disease experienced a PFS event and the PFS was shorter than those without baseline CNS disease (13.6 months, 95% CI: 4.5-NE). For the 20 patients with CNS disease at baseline, the median intracranial PFS was 7.7 months (95% CI: 3.8, 19.3). The PFS event-free rates at six, nine, 12, and 18 months were 80% (95% CI: 68%-91%), 69% (95% CI: 56%-82%), 65% (95% CI: 51%-78%), and 52% (95% CI: 36%-68%), respectively.[3]

Results from sensitivity analyses for PFS were consistent with the results from the primary PFS analysis. With additional censoring for missing tumour assessment and new non-protocol anti-cancer therapy, PFS was 19.0 months (95% CI: 12.2, 36.6) and 19.0 months (95% CI: 13.6, 36.6), respectively.[17]

As of May 31, 2018, 41 patients were deemed to have a clinical benefit out of the 53 patients, corresponding to a CBR of 77% (95% CI: 64-88%).[17]

For the May 31, 2018 cut-off, 18 (34%) patients experienced a CNS progression event at the time of data cut-off date; two new lesions, 10 disease progressions, and six deaths were observed. The median time to CNS progression was not estimable (NE) (95% CI: 15.1, NE) for the 53 patients with a median follow-up for progression or death of 15.5 months (25th percentile: 8.3, 75th percentile: NE; range: 0 to 42).[2,3]

As per the May 31, 2018 cut-off including 53 patients, nine (17%) patients had died. The median OS was NE (95% CI: NE; 25th percentile: NE, 75th percentile: NE; range: 0.8 to 43.1). The OS event-free rates at six, nine, 12, and 18 months were 92% (95% CI: 84%-100%), 87% (95% CI: 78%-97%), 85% (95% CI: 74%-95%), and 82% (95% CI: 70%-93%), respectively.[3]

Table 22: Summary of response outcomes as per BICR assessment in the ROS-1 Efficacy Evaluable Analysis Set, n = 53

	Integrated efficacy-evaluable population (n=53)	Patients with baseline CNS disease (n=23)*	Patients with no baseline CNS disease (n=30)*
Objective responses, n; % (95% CI)	41; 77% (64–88)	17; 74% (52–90)	24; 80% (61–92)
Best overall response			
Complete response, n (%)	3 (6%)†	0	3 (10%)
Partial response, n (%)	38 (72%)†	17 (74%)	21 (70%)
Stable disease, n (%)	1 (2%)	0	1 (3%)
Progressive disease, n (%)	4 (8%)	4 (17%)	0
Non-complete response or non-progressive disease, n (%)	3 (6%)	0	3 (10%)
Missing or unevaluable, n (%)‡	4 (8%)	2 (9%)	2 (7%)
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)
Intracranial activity	..	20·0‡	..
Overall response, n; % (95% CI)	..	11; 55% (32–77)	..
Best intracranial response			
Complete response, n (%)	..	4 (20%)	..
Partial response, n (%)	..	7 (35%)	..
Stable disease, n (%)	..	0	..
Progressive disease, n (%)	..	3 (15%)	..
Non-complete response or non-progressive disease, n (%)	..	4 (20%)	..
Missing or unevaluable, n (%)§	..	2 (10%)	..

Shown are the proportion of patients achieving a response, duration of response, and progression-free survival (RECIST version 1.1 by blinded independent central review) in the integrated efficacy population (patients with *ROS1* fusion-positive and ROS1 inhibitor-naive non-small-cell lung cancer) and intracranial response, duration of response, and progression-free survival in patients with CNS disease at baseline (RECIST version 1.1, according to blinded independent central review). NE=not estimable. RECIST=Response Evaluation Criteria in Solid Tumors. *CNS disease status determined by investigator. †These percentages do not equal 77% due to rounding. ‡CNS disease status determined by BICR. §Missing or unevaluable included patients with no post-baseline scans available, missing subsets of scans, or patients who discontinued before obtaining adequate scans to evaluate or confirm response.

Table 2: **Efficacy outcomes**

Source: Reprinted from the Lancet Oncology, 21(2), Drilon A et al, entrectinib in ROS-1 fusion positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials, pages 261-270, Copyright (2020), with permission from Elsevier[2]

Figure 4: Kaplan Meier Curves for DOR, PFS, OS, time to CNS progression

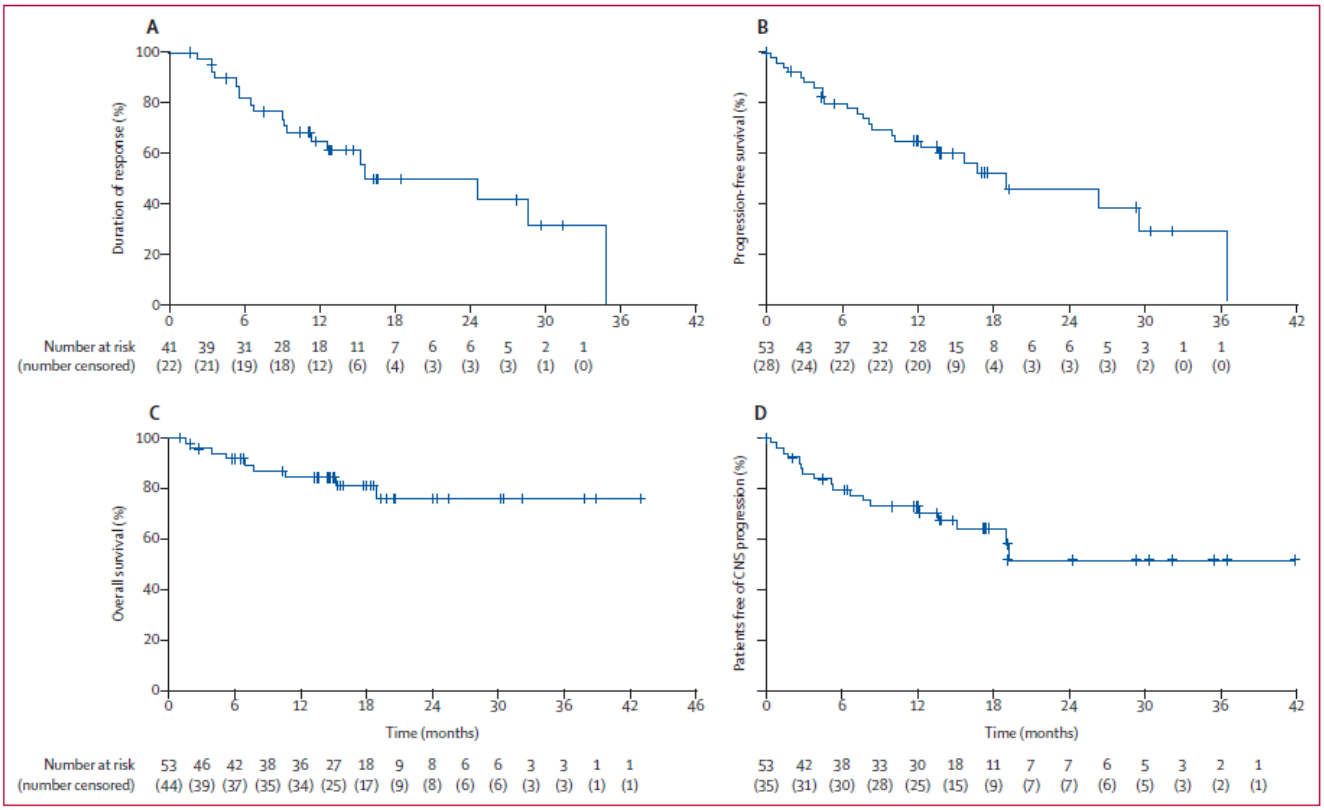


Figure 2: **Time-to-event analyses**
Kaplan–Meier curves of (A) duration of response, (B) progression-free survival, (C) overall survival, and (D) time to CNS progression. All assessments shown were based on blinded independent central review. Tick marks indicate censored patients.

Source: Reprinted from the Lancet Oncology, 21(2), Drilon A et al, entrectinib in ROS-1 fusion positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials, pages 261-270, Copyright (2020), with permission from Elsevier[2]

Results from additional data cut-offs

October 31, 2018 data cut-off: N = 53: With an additional 5 months of follow-up, the results at the October 31, 2018 data cut-off date were consistent with the response rates seen at the May 31, 2018 data-off date. For the October 31 2018 cut-off, there was a median duration of follow-up from the first response of 20.5 months (95% CI: 17.6, 21.0) and median duration of survival of 20.6 months (95% CI: 18.4, 23.0) for the 53 patients in the ROS-1 NSCLC Efficacy Evaluable Analysis Set.[3,21] The ORR was 79.2% (95% CI: 65.9-89.2%), which was achieved in 42 patients; five with a CR and 37 with a PR. The ORR was 73.9% (95% CI: 52, 90) for CNS at baseline and 83% (95% CI: 65, 94) for those without CNS at baseline. The DOR was a median of 24.6 months (95% CI: 12.6, 34.8) with 21 of 42 responders experiencing an event.[3] For the 23 patients with CNS disease at baseline, 17 were responders and 6 experienced a death (4 with progressive disease and 2 died), with a median DOR of 12.6 months (95% CI: 6.5, NE).[3] For the 30 patients without CNS disease at baseline, 24 were responders and 13 had events (12 with progressive disease and 1 died) with a median DOR of 24.6 months (95% CI: 11.4, 34.8).[3] In the updated analysis as of October 2018, four patients experienced a CR and seven patients experienced a PR, with an updated IC-ORR of 55% (95% CI: 32-77%). The median BICR IC-DOR was 12.9 months (95% CI: 5.6, NE) with five event-free patients. The median BICR IC PFS was 7.7 months (95% CI: 3.8, 13.6). The CBR was 79.2% (95% CI: 65.9-89.16%), with five patients experiencing a CR, 37 a PR, one with stable disease, four with progressive disease, two with non-CR or progressive disease and four patients with missing or unevaluable data.[3]

For the 23 patients with CNS at baseline, ORR was 73.9% (95% CI: 51.6-89.8%), with one patient experiencing CR, 16 PRs, four progressive disease, and two with missing or unevaluable data. In contrast, for the 30 patients deemed as not having CNS at baseline, the ORR was 83.3% (95% CI: 65.3-94.4%), with four CRs, 21 PRs, one with stable disease, two non-CR or progressive disease, and two with missing or unevaluable data. The time to CNS progression was a median of 30.8 months (95% CI: 15.1, NE; 25th percentile: 8.3, 75% percentile: NE, range: 0 to 42) with 22 patients experiencing events; two first new CNS lesions, 11 disease progressions, and nine deaths (31 out of 53 patients without events). Event free rates for time to CNS progression by BICR assessment were provided. At 6 months, there were 39 patients remaining at risk with an event free probability for CNS progression of 0.80 (95% CI: 0.69, 0.91), which was 34 patients at 9 months (0.74, 95% CI: 0.61, 0.86), 32 patients at 12 months (0.71, 95% CI: 0.59, 0.84), and 23 patients at 18 months (0.62, 95% CI: 0.48, 0.76).[3] There were 30 patients (75%) who experienced a DOR ≥6 months, 28 (70%) for ≥9 months, 22 (55%) for ≥12 months, and 12 (30%) for ≥18 months.[11] The PFS was a median of 19 months (95% CI: 12.2, 29.6; 25 events: 20 progressive disease and 5 deaths) for the overall sample and 13.6 months (95% CI: 4.5, NE; 11 events: 8 progressive disease and 3 deaths) for patients with CNS disease at baseline and 26.3 months (95% CI: 15.7, 36.6; 14 events: 12 progressive disease and 2 deaths) for patients without CNS disease at baseline. The intracranial PFS for 14 patients with events (11 disease progressions and 3 deaths) was a median of 7.7 months (95% CI: 3.8, 13.6, 25th percentile: 3, 75th percentile: 19.3, range 0 to 19.4).[28] The OS was not estimable at the October 30, 2018 cut-off (95% CI: 30.8, NE).[3]

May 1, 2019 data cut-off; N = 94: The updated results at the May 1, 2019 data cut-off date are based on a larger efficacy evaluable population of 94 patients who at this data cut-off point all had more than 12 months of efficacy follow-up (follow-up time since onset of first response) as per the defined criterium for the pre-specified final data cut-off date (May 31, 2018). Overall, the efficacy results of the broader population of 94 patients with ROS-1 NSCLC at the time of May 1, 2019 data cut-off date demonstrate consistency with the results reported for the 53 patients at the time of the May 31, 2018 and October 31, 2018 data cut-off dates. The results continue to suggest durable responses in a high proportion of patients, including intracranial responses in patients with CNS disease at baseline. With regards to comparing the results across all three data cut-off dates and subpopulations to assess the consistency of efficacy results, differences in follow-up duration (see Table 23) and patient characteristics (less favorable in the = 41 data set, see section 6.3.2.1, c) Populations) should be considered when comparing results between these populations.

Table 23: Subpopulations of the efficacy evaluable population and follow-up times at respective data cut-off dates

Subpopulations	May 1, 2018	Oct 31, 2017	May 1, 2019
N = 53 median duration of follow-up from the time of first response, months (95%CI) median survival follow-up, months (95%CI)	16.6 (13.8, 17.9) 15.5 (14.8, 19.0)[2]	20.5 months (17.6, 21) 20.6 (18.4, 23.0)	25.4 (not reported) 25.9 (23.9, 28.8).
N = 41 median duration of follow-up from the time of first response, months (95%CI) median survival follow-up, months (95%CI)	N/A	N/A	18.9 (not reported) 19.8 (18.2, 20.3)
N = 94 median duration of follow-up from the time of first response, months (95%CI) median survival follow-up, months (95%CI)	N/A	N/A	20.3 (19.2, 22.8) 20.9 (19.8, 23.9)

N/A = not applicable

Source: Drilon, 2020[2] and Submission material[3]

Table 24 shows key results for the 94 patients with measurable disease enrolled before 30 November 2017 along with the populations of the primary Efficacy Evaluable Analysis Set (n = 53 patients enrolled up to 30 April 2017) and the complementary dataset (n = 41 patients enrolled after 30 April and up to 30 November 2017).

With an additional 11 months of follow-up and an additional 41 patients (complementary efficacy evaluable data set) totalling 94 patients, the median duration of follow up from the time of first response was 20.3 months (95% CI: 19.2, 22.8) and the median duration of survival follow-up was 20.9 months (95% CI: 19.8, 23.9). Patients enrolled in the complete data set (n = 41) who were enrolled between 30 April 2017 and 30 November 2017, had a shorter survival follow-up (19.8 months) than the initial 53 patients in the primary dataset enrolled up to 30 April 2017 (25.9 months).[3] The ORR was 73.4% (95% CI: 63.3, 82.0) for the N = 94 set. The BOR included 69 patients, 11 with a CR and 58 with a PR. Six patients had stable disease (6.4%), eight had progressive disease (8.5%), three had a non-complete response or non-progressive disease (3.2%), and 8 had missing or unevaluable data (8.5%). The median DOR was 16.5 months (95% CI: 14.6, 28.6). The PFS was a median of 16.8 months (95% CI: 12.0, 21.4), with 54 patients (57.4%) experiencing the event. Sensitivity analyses for PFS assessed by investigator assessment were consistent with the initial results for PFS by BIRC, with 14.5 months (95% CI: 10.0, 17.4).[3] For 40 patients determined as having CNS disease at baseline as per investigator, the ORR was 67.5% (95% CI: 50.9, 81.4), with 27 patients with a confirmed CR or PR, including four with a CR, 23 with a PR, two with stable disease, six with progressive disease, and five with missing or unevaluable data. The CBR was 74.5% (95% CI: 64, 83; 70 patients deemed as having a clinical benefit). The ORR was analyzed by the number of prior systemic therapies received by the patients. For the 31 patients without previous therapy, the ORR was 83.9% (95% CI: 66, 95), which decreased to 63.2% for 38 patients with one previous therapy (95% CI: 46, 78). The ORR was 69% for 13 patients receiving two therapies (95% CI: 39, 91) and 100% for four patients receiving three or more therapies (95% CI: 40, 100).[3]

Results for CNS disease at baseline are presented in Table 25. The intracranial ORR for those 34 patients with measurable and non-measurable CNS disease at baseline was 50% (95% CI: 32.4, 67.6), with an intracranial DOR of 12.9 months (5.6, 22.1) and an intracranial PFS of 7.7 months (4.6, 15.7) among 25 patients experiencing the event. The time to CNS progression was 24.8 months (95% CI: 16.1, NE). Twenty-five patients died (26.6%), with a median OS that was NE (95% CI: 28.3, NE). Most patients achieved their first response at or before the first 4-week cycle.[3]

With an additional 11 months of follow-up, the results at the May 1, 2019 data cut-off date for the subpopulation of 53 patients were consistent with results seen at the May 31, 2018 data-off date. For the 53 patients, the median duration of survival follow-up was 25.9 months (95% CI: 23.9, 28.8). The ORR increased to 79.2% (95% CI: 65.9, 89.2), with 42 experiencing a response (BOR: 5 complete response and 37 partial response) and CBR of 79.2% (95% CI: 65.9, 89.2). One patient had stable disease (1.9%), 4 had progression disease (7.5%), 2 had a non-complete response or non-progressive disease (3.8%), and 4 had missing or unevaluable data (7.5%). The median DOR was 20.5 months (95% CI: 12.6, 34.8). Event free rates for time to CNS progression by BICR assessment were provided. Overall, 82% (95% CI: 70, 94) of the patients had an event-free DOR at 6 months and 66% (95% CI: 51, 81) of the patients had an event-free DOR at 12 months. The number of patients experiencing a lasting response at 6 or more months was 31 (58.5%) and 23 (43.4%) for 12 or more months. The PFS was a median of 19 months (95% CI: 12.2, 29.6) with 30 patients (56.6%) experiencing the event. For 18 patients deemed as having measurable CNS disease, there were 14 responders with an IC-ORR of 77.8% (95% CI: 52, 94) and two patients experienced CR, 12 PR, two had progressive disease, and two had missing or unevaluable data. The IC-DOR was a median of 12.9 months (95% CI: 5.3, 16.5) and IC-PFS was 7.7 months (95% CI: 4.6, 17.4).[3]

Table 26 outlines intracranial ORR and duration of intracranial response by prior brain radiation. Nine had no brain radiation prior to study entry (7 responders, IC-ORR of 77.8%; 95% CI: 40, 97; IC-DOR 11.1 months; 95% CI: 3.7, 12.9), 8 had prior radiation for 2 months or less (7 responders, IC-ORR of 87.5%; 95% CI: 47, 100; IC-DOR 14.7 months; 95% CI: 5.3, 22.1), one had radiation therapy for more than 2 months (0 responders, IC-ORR of 0%; 95% CI: 0, 98; IC-DOR NA), and 10 had no brain radiotherapy or brain radiotherapy for more than 2 months (7 responders, IC-ORR of 70%; 95% CI: 35, 93; IC-DOR 11.1 months; 95% CI: 3.7, 12.9). For 34 patients deemed as having both measurable and non-measurable CNS disease, 17 were responders (5 CR, 12 PR, 5 progressive disease, 9 non-CR or progressive, 3 missing or unevaluable). Seventeen measurable and non-measurable patients had no brain radiation prior to study entry (8 responders, IC-ORR of 47.1%; 95% CI: 23, 72; IC-DOR 11.1 months; 95% CI: 3.7, NE), 12 had prior radiation for 2 months or less (9 responders, IC-ORR of 75%; 95% CI: 43, 95; IC-DOR 14.7 months; 95% CI: 5.3, 22.1), 5 had radiation therapy for more than 2 months (0 responders, IC-ORR of 0%; 95% CI: 0, 52; IC-DOR NA), and 22 had no brain

radiotherapy or brain radiotherapy for more than 2 months (8 responders, IC-ORR of 36.4%; 95% CI: 17, 59; IC-DOR 11.1 months; 95% CI: 3.7, NE). The time to CNS progression was a median of 25.6 months (95% CI: 15.1, NE). Fourteen patients had(26.4%) died, with an overall OS that was NE (95% CI: 28.3, NE).[3]

Health Canada Review Report Conclusion

In the Health Canada report[21] it was concluded that the October 31, 2018 results were consistent with those presented in the May 31, 2018 integrated analysis. The results for the May 31, 2018 cut-off were also consistent with those provided for the May 31, 2019 cut-off, with small variations.

Table 24: Summary of response outcomes as per BICR assessment in the ROS-1 Efficacy Evaluable Analysis Set for the May 31, 2018 and May 1, 2019 cut-offs

Table 3 Overview of Updated Efficacy in Patients with ROS1-Positive NSCLC as Assessed by BICR (CCOD: 1 May 2019)

	Primary ROS1 NSCLC Efficacy Evaluable	Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
enrolment cutoff date	30 April 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
clinical cut-off date	31 May 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled	**N=53**	**N=53**	**N=41**	**N=94**
Median duration of survival follow-up, months (95% CI)	15.5 (14.8, 19.0)	25.9 (23.9, 28.8)	19.8 (18.2, 20.3)	20.9 (19.8, 23.9)
Primary Endpoints				
Objective Response (ORR)[a]				
Patients with confirmed CR or PR, n	41	42	27	69
ORR, % (95% CI)[b]	77.4% (63.8, 87.7)	79.2% (65.9, 89.2)	65.9% (49.4, 79.9)	73.4% (63.3, 82.0)
Best Overall Response (BOR)[a]				
Complete Response, n (%)	3 (5.7%)	5 (9.4%)	6 (14.6%)	11 (11.7%)
Partial Response, n (%)	38 (71.7%)	37 (69.8%)	21 (51.2%)	58 (61.7%)
Stable Disease, n (%)	1 (1.9%)	1 (1.9%)	5 (12.2%)	6 (6.4%)
Progressive Disease, n (%)	4 (7.5%)	4 (7.5%)	4 (9.8%)	8 (8.5%)
Non CR/PD, n (%)	3 (5.7%)	2 (3.8%)	1 (2.4%)	3 (3.2%)
Missing or unevaluable, n (%)	4 (7.5%)	4 (7.5%)	4 (9.8%)	8 (8.5%)

		Primary ROS1 NSCLC Efficacy Evaluable	Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
enrolment cutoff date		30 April 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
clinical cut-off date		31 May 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled		**N=53**	**N=53**	**N=41**	**N=94**
Duration of Response (DOR)[a]					
Patients with event/confirmed CR or PR (%)		19/41 (46.3%)	22/42 (52.4%)	14/27 (51.9%)	36/69 (52.2%)
Median, months (95% CI)[c]		24.6 (11.4, 34.8)	20.5 (12.6, 34.8)	16.5 (11.1, NE)	16.5 (14.6, 28.6)
Event-free probability (95% CI)[c]	6 months[d]	0.82 (0.70, 0.94)	0.82 (0.70, 0.94)	0.81 (0.67, 0.96)	0.82 (0.72, 0.91)
	12 months[d]	0.65 (0.49, 0.81)	0.66 (0.51, 0.81)	0.66 (0.48, 0.84)	0.66 (0.54, 0.78)
No. of patients with responses lasting:	≥6 months	31 (58.5%)	31 (58.5%)	22 (53.7%)	53 (56.4%)
n (%)	≥12 months	18 (34.0%)	23 (43.4%)	17 (41.5%)	40 (42.6%)
Secondary Endpoints					
Clinical Benefit Rate (CBR)[a]		41	42	28	70
CBR (95% CI)[b]		77.4% (63.8, 87.7)	79.2% (65.9, 89.2)	68.3% (51.9, 81.9)	74.5% (64.4, 82.9)
Progression-Free Survival (PFS)[a]					
Patients with event, n (%)		25 (47.2%)	30 (56.6%)	24 (58.5%)	54 (57.4%)
Median, months (95% CI)[c]		19.0 (12.2, 36.6)	19.0 (12.2, 29.6)	15.5 (6.4, 21.1)	16.8 (12.0, 21.4)
Time to CNS Progression[a]					
Median, months (95% CI)[c]		NE (15.1, NE)	25.6 (15.1, NE)	NE (15.7, NE)	24.8 (16.1, NE)

	Primary ROS1 NSCLC Efficacy Evaluable	Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1 NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
enrolment cutoff date	30 April 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
clinical cut-off date	31 May 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled	**N=53**	**N=53**	**N=41**	**N=94**
Overall Survival (OS)				
Patients with event, n (%)	9 (17.0%)	14 (26.4%)	11 (26.8%)	25 (26.6%)
Median, months (95% CI)[c]	NE (NE, NE)	NE (28.3, NE)	NE (NE, NE)	NE (28.3, NE)

NE, not estimable.

[a] All endpoints based on tumor response and progression were by blinded independent central review (BICR) as per RECIST v1.1 criteria.

[b] 95% CIs for proportions calculated using the Clopper-Pearson method.

[c] Median and percentiles for time-to-event analyses based on Kaplan-Meier estimates. Confidence Intervals (CI) for the median were computed using the method of Brookmeyer and Crowley.

[d] Event-Free Probabilities are Kaplan-Meier estimates and confidence intervals were calculated using the method of Kalbfleisch and Prentice.

Source: Table 10 of SCE; t_ef_fudur_REENDA; t_ef_fudur_REE3NDA; t_ef_fudur_REE4NDA; t_ef_boricr_REENDA; t_ef_boricr_REE3NDA; t_ef_boricr_REE4NDA; t_ef_km_OBJRDRR1_REENDA; t_ef_km_OBJRDRR1_REE3NDA; t_ef_km_OBJRDRR1_REE4NDA; t_ef_cbricr_REENDA; t_ef_cbricr_REE3NDA; t_ef_cbricr_REE4NDA; t_ef_km_PFSRAD1_REENDA; t_ef_km_PFSRAD1_REE3NDA; t_ef_km_PFSRAD1_REE4NDA; t_ef_km_CNSPFS_REENDA; t_ef_km_CNSPFS_REE3NDA; t_ef_km_CNSPFS_REE4NDA; t_ef_km_OS_REENDA; t_ef_km_OS_REE3NDA; t_ef_km_OS_REE4NDA.

Source: Submission documents[3]

Table 25: Overview of Updated Intracranial Efficacy of Entrectinib in Adult Patients with ROS-1 positive NSCLC and CNS Disease at Baseline as Assessed by BICR May 1, 2019 data cut-off date

	Primary ROS1 NSCLC Efficacy Evaluable	Primary ROS1 NSCLC Efficacy Evaluable	Complementary ROS1NSCLC Efficacy Evaluable	Overall ROS1 NSCLC Efficacy Evaluable
enrollment cutoff date for patients included	30 April 2017	30 April 2017	30 April 2017 to 30 November 2017	30 November 2017
clinical cutoff date for analysis	31 May 2018	1 May 2019	1 May 2019	1 May 2019
Total no. of patients enrolled	**N=53**	**N=53**	**N=41**	**N=94**
Patients with CNS Metastases at Baseline by BICR	**(N=20)**	**(N=20)**	**(N=14)**	**(N=34)**
Intracranial Objective Response Rate[a]				
Responders (CR or PR), n	11	11	6	17
IC-ORR, % (95% CI)[b]	55.0% (31.5, 76.9)	55.0% (31.5, 76.9)	42.9% (17.7, 71.1)	50.0% (32.4, 67.6)
Intracranial Duration of Response[a]				
No. of patients with events, n (% of responders)	5/11 (45.5%)	7/11 (63.6%)	4/6 (66.7%)	11/17 (64.7%)
Median, months (95% CI)[c]	12.9 (5.6, NE)	12.9 (5.6, NE)	12.9 (3.7, NE)	12.9 (5.6, 22.1)
Intracranial Progression-Free Survival[a]				
No. of patients with events, n (%)	13 (65.0%)	15 (75.0%)	10 (71.4%)	25 (73.5%)
Median, months (95% CI)[c]	7.7 (3.8, 19.3)	7.7 (3.8, 13.6)	13.8 (2.7, 17.4)	7.7 (4.6, 15.7)

NE, not estimable.

[a] All endpoints based on tumor response and progression were by blinded independent central review (BICR) as per RECIST v1.1 criteria.

[b] 95% CIs for proportions calculated using the Clopper-Pearson method.

[c] Median and percentiles for time-to-event analyses based on Kaplan-Meier estimates. Confidence Intervals (CI) for the median were computed using the method of Brookmeyer and Crowley.

Source: Submission documents[3]

Table 26: Intracranial ORR and Duration of Intracranial Response (BIRC Assessment) by Prior Brain Radiation

	BICR-confirmed CNS Disease at Baseline			
	Measureable		Measureable + Non Measureable	
	N=18		N=34	
Intracranial ORR[a]				
Brain radiation status and timing relative to study entry:	no. patients included in analysis	Responders (PR or CR), n (%) (95% CI)[b]	no. patients included in analysis	Responders (PR or CR), n (%) (95% CI)[b]
No brain RT	n=9	7 (77.8%) (40.0%, 97.2%)	n=17	8 (47.1%) (23.0%, 72.2%)
≤2 months	n=8	7 (87.5%) (47.4%, 99.7%)	n=12	9 (75.0%) (42.8%, 94.5%)
>2 months	n=1	0 (0.0%, 97.5%)	n=5	0 (0.0%, 52.2%)
No brain RT or brain RT >2 months	n=10	7 (70.0%) (34.8%, 93.3%)	n=22	8 (36.4%) (17.2%, 59.3%)
Total	**n=18**	**14 (77.8%) (52.4%, 93.6%)**	**n=34**	**17 (50.0%) (32.4%, 67.6%)**
Intracranial DoR[a]				
Brain radiation status and timing relative to study entry:	no. patients with event/ no. of responders (%)	median months (95% CI)[c]	no. patients with event/ no. of responders (%)	median months (95% CI)[c]
No brain RT	5/7 (71.4%)	11.1 (3.7, 12.9)	5/8 (62.5%)	11.1 (3.7, NE)
≤2 months	5/7 (71.4%)	14.7 (5.3, 22.1)	6/9 (66.7%)	14.7 (5.3, 22.1)
>2 months	0	N/A	0	N/A
No brain RT or brain RT >2 months	5/7 (71.4%)	11.1 (3.7, 12.9)	5/8 (62.5%)	11.1 (3.7, NE)
Total	**10/14 (71.4%)**	**12.9 (5.3, 16.5)**	**11/17 (64.7%)**	**12.9 (5.6, 22.1)**

Source: Submission documents[3]

Quality of Life

HRQoL was only evaluated in the STARTRK-2 trial. Patient reported outcomes data were analyzed at the May 31, 2018 and May 1, 2019 data cut-off dates. HRQoL results were overall consistent between data cut-off dates. Due to the small number of patients (n = 37) available at the May 31, 2018 data cut, this CADTH report focuses on the results from the May 1, 2019 data cut-off date with 78 patients providing HRQoL data. For the May 1, 2019 data cut-off date, all patients in the expanded ROS-1 Efficacy Evaluable Analysis Set from STARTRK-2 (n = 78) completed at least one question in the EORTC QLQ-C30 questionnaire and all except one patient completed at least one question in the QLQ-LC13 instruments. HRQoL assessments were administered prior to the first dose of entrectinib at Cycle 1 (Day 1) and for each subsequent cycle (Day 1), as well as at the end of treatment.[11] The compliance rate was relatively high for the QLQ-C30 and QLQ-LC30 questionnaires with at least 80% of patients completing at least one question out of patients expected to complete questionnaires at most study visits.[3] However, the number of patients available to provide patient-reported outcomes data declined gradually over the course of the study. At cycle 18 approximately 50% out of 78 patients completed the QLQ-C30 and QLQ-LC13 questionnaires. At cycle 24 (after approximately 2 years of entrectinib treatment) approximately 25% of patients completed the questionnaires.[3] Interpretation of changes from baseline is limited by the high patient drop-off at later cycles.

At baseline, the Global Health Status/QoL and Functional Scale scores were moderate-to-high and showed higher values compared to the baseline value (higher scores reflecting improvement) at most assessment points, except the cognitive functioning scale which showed worsening scores at most assessment points.

- The mean score at baseline for the Global Health Status/QoL instrument was 54.91 (SD 24.78) and gradually increased with the highest scores occurring between cycles 8 and 17 (mean scores between 71.47 [SD 15.94] and 73.08 [SD 16.05]). After cycle 17 scores declined gradually but remained above the baseline value. Mean changes from baseline ranged from 0.64 (DS 24.93) to 12.5 (SD 25.29) up to Cycle 22 with mean changes at specific timepoints being above the clinical meaningful threshold of a 10-point change (e.g., better mean change scores of 12.50 [SD 25.29] at Cycle 5, and of 12.18 [SD 23.07] at Cycle 8). From Cycle 23 and beyond, there were only 18 patients who were still completing the questionnaires. Due to the small number of patients proving data the interpretation of the scores at later cycles is limited.

- The mean score at baseline for the Physical Functioning score was 68.06 (SD 22.60) and overall increased with scores at most assessment points fluctuating around a mean score of 80±3. From Cycles 1 up to Cycle 22 the highest mean score occurring at Cycle 9 was 84.05 (SD 18.04). Mean changes from baseline ranged from 4.11 (SD 21.81) to 10.42 (SD 20.33) up to Cycle 22.
- The mean score at baseline for the Role Functioning scale was 60.68 (SD 28.17) and overall increased with scores at most assessment points fluctuating around a mean score of 72±3. From Cycle 1 up to Cycle 22 the highest score occurring at Cycle 13 was 78.15 (SD 25.08). The mean changes from baseline ranged from 0.00 (SD 28.87) to 9.90 (SD 25.32) up to Cycle 22.
- The mean score at baseline for the Cognitive Functioning scale was 81.84 (SD 18.45) and overall declined with scores at most assessment points fluctuating around a mean score of 77±3. From Cycle 1 up to Cycle 22 the highest score occurring at Cycle 13 was 82.91 (SD 17.72). Worsening mean changes from baseline were reported ranging from – 2.08 (SD 24.40) to -11.54 (SD 23.93) up to Cycle 22 with mean changes at specific timepoints being above the clinical meaningful threshold of a 10-point change (e.g., worse mean change scores of -11.54 [SD 23.93] at Cycle 21, and of -10.61 [SD 23.13] at Cycle 19).[3]

For the QLQ-LC13 instrument, patients reported lung symptom burden at baseline with trends towards improvement.

- The mean score at baseline for the coughing symptom scale was 38.53 (SD 26.53) and overall decreased (lower scores indicate improvement) with scores at most assessment points fluctuating around a mean score of 16±3. From Cycle 1 up to Cycle 22, the lowest mean score occurring at Cycle 22 was 8.00 (SD 14.53). The mean changes from baseline ranged from -29.17 (SD 33.06) to -12.31 (SD 27.99) up the Cycle 22 with most mean changes being above the clinical meaningful threshold of a 10-point change. Up to 66.7% of patients reported clinically meaningful improvements for coughing (≥10 point change in the symptoms subscale score) at any post-baseline assessment timepoint with imminent improvements in cough from baseline scores of 38.5 (mean change of -12.3 on Cycle 2 Day 1).
- The mean score at baseline for dyspnea was 35.93 (SD 25.10) and overall decreased with scores at most assessment points fluctuating around a mean score of 23±3. From Cycle 1 up to Cycle 22, the lowest mean score occurring at Cycle 20 was 20.83 (SD 17.57). The mean changes from baseline ranged from -12.28 (SD 27.51) to -4.97 (SD 26.43) up to Cycle 22 with most mean changes being above the clinical meaningful threshold of a 10-point change.
- The mean score at baseline for the chest pain symptom scale was 18.18 (SD 22.00) and overall decreased with scores at most assessment points fluctuating around a mean score of 8±3. From Cycle 1 up to Cycle 22, the lowest mean score occurring at Cycle 19 was 5.05 (SD 14.72). The mean changes from baseline ranged from -10.75 (SD 21.57) to -1.08 (SD 23.54) with mean changes at specific timepoints being above the clinical meaningful threshold of a 10-point change (e.g., better mean change scores of -10.75 [SD 21.57] at Cycle 3 and of -10.56 [SD 25.67] at Cycle 4).[3]

Results were also provided by the sponsor for the EQ-5D Visual Analogue Scale (VAS) based on a larger sample (n = 145) with ROS-1 positive patients from the STARTRK-2 trial. The exact criteria for defining the 145 patients were not provided. On Cycle 1 Day 1, 100% of 145 patients responded to the EQ-5D VAS. This number reduced to 28.3% at cycle 18 and 14.5%% for Cycle 23 Day 1. After cycle 26, less than 10 people provided results and therefore the mean values were no longer considered robust. The mean score at baseline was 64.91 (SD 20.55) and overall increased (higher scores reflecting improvement) with scores at most assessment points fluctuating around a mean score of 77±2 up to cycle 22. From Cycle 1 up to Cycle 22, the highest mean score occurring at Cycle 15 was 78.46 (SD 16.07). The mean changes from baseline were not provided.[28] From Cycle 23 and beyond, there were only 18 patients who were still completing the questionnaires. Due to the small number of patients proving data the interpretation of the scores at later cycles is limited.[28]

Safety

Overall Safety Populations, n = 355, n = 134 – May 31, 2018 cut-off: An overview of the adverse events (AEs) in the integrated Overall Safety Analysis Population (n = 355) and the ROS-1 NSCLC Safety set (n = 134) can be found in Table 27. Overall incidence and severity of AEs as well as the percentages of patients discontinuing treatment due to AEs was similar between the two safety sets.[11]

In the n = 355 set, almost all patients (99%) experienced at least one AE. AEs of any Grade occurring most frequently included fatigue (48%), constipation (46%), dysgeusia (44%), dizziness (38%), edema (40%), diarrhea (35%), nausea (34%), dysesthesia (34%), dyspnea (30%), cough (24%), cognitive impairment (27%), peripheral sensory neuropathy and headache (18% each), ataxia (17%) and mood disorders (10%). The majority of patients (61%) experienced AEs of Grade 3 or 4. AEs of Grade 3 or 4 occurring most frequently included anemia (9%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), pneumonia, pulmonary embolism, hypoxia, and AST increased (each 3.4%), cognitive impairment (4.5%), pleural effusion and AST increased (each 3.1%), hypotension/orthostatic hypotension and hypophosphatemia (each 2.8%), neutropenia and syncope (each 2.5%), UTI (2.3%),

diarrhea, hypokalemia, hyponatremia, and lipase increased (2.0%).[11] Serious AEs occurred in 39% of patients. A total of 99% of patients experienced treatment-related AEs and 9% experienced treatment related serious AEs.

AEs leading to discontinuation occurred in 9%, whereas 28% experienced an AE leading to dose reduction and 46% experienced an AE leading to drug interruption. Six percent of patients experienced an AE leading to death.

In the n = 133 set, all ROS-1 fusion positive patients (100%) experienced an AE, and 61% experienced an AE considered to be Grade 3 or 4. Serious AEs occurred in 37% of patients. A total of 100% of patients experienced a treatment related AEs and 13% experienced treatment related serious AEs.

AEs leading to discontinuation occurred in 9% of patients, whereas 34% experienced an AE leading to dose reduction and 45% experienced an AE leading to drug interruption. Seven percent of patients experienced an AE leading to death.

Table 27: Summary of adverse events in the integrated Safety Population and by subgroup – May 31, 2018 cut-off date

	NTRK **Adult (n=68)**	***ROS1*** **NSCLC Adult (n=133)**	**Other Adult non*NTRK*, non*ROS1* (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Patients with AE (%)	100	100	99	100	99
Patients with treatment related AE (%)	100	100	98	100	99
Patients with SAE (%)	47	37	40	13	39
Patients with related SAE (%)	10	13	5	6	9
Patients with ≥Grade 3 AE (%)	74	61	56	50	61
Patients with AE leading to discontinuation (%)	13	9	6	6	9
Patients with AE leading to dose reduction (%)	41	34	16	25	28
Patients with AE leading to drug interruption (%)	56	45	43	38	46
Patients with AE leading to death (%)	9	7	4	0	6

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Note: It was stated in the FDA report[11] that it was incorrectly indicated that there were 134 patients within the ROS-1 positive NSCLC bucket, whereas the corrected number is n = 133. Information from the FDA report that is included within this CADTH CGR reports n = 133 instead of n = 134.

The types of treatment -related AEs occurring in patients in the ROS-1 Safety set (n = 133) are displayed in Table 28. The majority of treatment related AEs were of Grade 1 or 2. Out of the 133 patients included in the safety analysis, the most common grade 1-2 treatment related AEs were dysgeusia (42%), dizziness (32%), constipation (33%), and diarrhea (26%). The most common grade 3 treatment related AEs were weight increase (7%), neutropenia (4%), neutrophil count decrease (2%), diarrhea (2%), myalgia (2%), aspartate aminotransferase increase (2%), and alanine aminotransferase increase (2%). There were a few Grade 4 treatment related AEs that occurred in the ROS-1 Adult Safety Population and included hyperuricaemia, blood creatine phosphokinase increase, limbic encephalitis, anorectal disorder and myocarditis (each n = 1, <1%).

Table 28: Treatment-related adverse events by grade, by ROS-1 fusion positive Safety Population (n = 134) – May 31, 2018 cut-off date

	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	19 (14%)	0	0
Blood creatinine increase	17 (13%)	1 (<1%)	0
Aspartate aminotransferase increase	14 (10%)	2 (2%)	0
Alanine aminotransferase increase	13 (10%)	3 (2%)	0
Hyperaesthesia	12 (9%)	1 (<1%)	0
Arthralgia	12 (9%)	1 (<1%)	0
Anaemia	11 (8%)	1 (<1%)	0
Hyperuricaemia	11 (8%)	0	1 (<1%)
Rash	9 (7%)	2 (1%)	0
Pruritus	9 (7%)	1 (<1%)	0
Peripheral sensory neuropathy	8 (6%)	1 (<1%)	0
Cognitive disorder	8 (6%)	1 (<1%)	0
Muscular weakness	6 (4%)	1 (<1%)	0
Hypotension	6 (4%)	1 (<1%)	0
Neutropenia	5 (4%)	5 (4%)	0
Neutrophil count decrease	5 (4%)	3 (2%)	0
Ataxia	5 (4%)	1 (<1%)	0
Pyrexia	5 (4%)	1 (<1%)	0
Dysarthria	4 (3%)	1 (<1%)	0
Pain of skin	4 (3%)	1 (<1%)	0
Lymphocyte count decrease	2 (1%)	1 (<1%)	0
Blood creatine phosphokinase increase	2 (1%)	1 (<1%)	1 (<1%)
Hypophosphataemia	2 (1%)	1 (<1%)	0
Orthostatic hypotension	2 (1%)	1 (<1%)	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0
Amylase increased	1 (<1%)	1 (<1%)	0
Dehydration	0	2 (1%)	0
Limbic encephalitis	0	0	1 (<1%)
Anorectal disorder	0	0	1 (<1%)
Myocarditis	0	0	1 (<1%)
Myoclonus	0	1 (<1%)	0
Hypoxia	0	1 (<1%)	0
Hypertension	0	1 (<1%)	0
Cardiac failure	0	1 (<1%)	0

The safety population includes all patients with *ROS1* fusion-positive NSCLC across the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). All treatment-related adverse events observed are shown. Data are n (%) of patients. Adverse events were encoded using Medical Dictionary for Regulatory Activities (version 21.0). NSCLC=non-small-cell lung carcinoma.

Source: Reprinted from the Lancet Oncology, 21(2), Drilon A et al, entrectinib in ROS-1 fusion positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials, pages 261-270, Copyright (2020), with permission from Elsevier[2]

Table 29 outlines the serious adverse events experienced in the Overall Safety Analysis Population (n = 355) and the ROS-1 NSCLC Safety set (n = 133). Incident and type of serious AEs were broadly similar between both sets. A total of 50 (37%) patients in the n = 133 set experienced a serious AE. Of these, 12% were associated with respiratory and mediastinal disorders, 10% were due to infections and infestations, 12% were associated with nervous system and psychiatric disorders, 4.5% were due to cardiac disorders, 2.2% due to vascular disorders, 3.0% due to gastrointestinal disorders, and 4.4% due to general disorders / administration site.

Table 29: Summary of serious adverse events (>1% total incidence), Safety-Evaluable Analysis Population – May 31, 2018 cut-off date

SOC/Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total n (%)	32 (47)	50 (37)	53 (39)	2 (13)	137 (39)
Respiratory and Mediastinal disorders	11 (16)	16 (12)	17 (12)	2 (13)	46 (13)
Dyspnea	2 (2.9)	6 (4.5)	5 (3.6)	0	13 (3.7)
Acute respiratory failure/respiratory distress	3 (4.4)	0	4 (2.9)	0	7 (2)
Pleural Effusion	3 (4.4)	5 (3.7)	3 (2.1)	2 (13)	12 (3.4)
Pulmonary embolism	2 (2.9)	3 (2.2)	3 (2.1)	0	8 (2.2)
Infections and Infestations	11 (16)	13 (10)	11 (8)	1 (6)	36 (10)
Pneumonia	2 (2.9)	2 (1.5)	10 (7)	0	14 (3.9)
Sepsis	2(2.9)	1 (0.7)	6 (4.4)	0	9 (2.5)
Nervous System Disorders and Psychiatric Disorder	8 (12)	16 (12)	11 (8)		35 (10)
Cognitive disorder	1 (1.5)	2(1.5)	2 (1.4)		5 (1.4)
Syncope	0 (0)	2 (1.5)	1 (0.7)		3 (0.8)
Ataxia	1 (1.5)	1 (0.7)	1 (0.7)		3 (0.8)
Dizziness	1 (1.5)	1 (0.7)	0		2 (0.6)
Mental status changes/confusion	1 (1.5)	2 (1.5)	3 (2.1)		5 (1.4)
Depression	1 (1.5)	0	0		1 (0.3)
Cardiac Disorders	5 (7)	6(4.5)	2 (1.4)		13 (3.7)
Vascular disorder	2 (2.9)	3(2.2)	2 (1.4)		7 (2)
Hypotension	2 (2.9)	3(2.2)	1		6 (1.7)
Gastrointestinal Disorder	0	4 (3)	10 (7)		14 (4)
General Disorders and administration site	2 (2.9)	6 (4.4)	7 (5)		15 (4.2)
Pyrexia	0	4 (3)	3 (2.1)		7 (2)

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

AEs leading to treatment discontinuation are highlighted in Table 30. In the n = 133 set, there were 9% of patients out of the 133 of the ROS-1 Safety Analysis set who had to discontinue treatment due to AEs. These were related to respiratory and mediastinal disorders (2%), 0.7% were due to infections and infestations, 1.5% were due to cardiac disorders, and 0.7% due to general disorders / administration site.[11]

Table 30: Summary of adverse events that led to treatment discontinuation in ≥1% patients, Safety-evaluable Analysis Population – May 31, 2018 cut-off date

SOC/Preferred Term	*NTRK* Adult (n=68)	*ROS1* NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	13	9	6	6	9
Respiratory and Mediastinal disorders					
Total	3	2	0.7	6	2.0
Dyspnea	0	0.7	0	6	0.6
Acute respiratory failure	3	0	0	0	0.6
Pneumonitis	0	0.7	0	0	0.3
Pulmonary edema	0	0	0.7	0	0.3
Pulmonary embolism	0	0.7	0	0	0.3
Cardiac Disorders					
Total	4.4	1.5	1.5	0	2.0
Cardio-respiratory arrest	2.9	0	0	0	0.6
CHF	1.5	0	0	0	0.3
A Fib/Extrasystoles	0	0	0.7	0	0.3
Myocarditis	0	0.7	0	0	0.3
Cardiogenic shock	0	0.7	0	0	0.3
Pericardial Effusion	0	0.7	0	0	0.3
Infections and Infestations					
Total	3	0.7	0.7	0	1.1
Pneumonia/Lower RTI/Lung infection	1.5	0.7	0.7	0	0.8
Sepsis	1.5	0	0	0	0.3
General disorders and administrative site conditions					
Total	1.5	0.7	1.5	0	1.1
Fatigue	1.5	0	0.7	0	0.6
Malaise	0	0	0.7	0	0.3
Peripheral edema	0	0.7	0	0	0.3

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

AEs leading to treatment interruption are highlighted in Table 31. There were 45% of patients out of the 133 of the ROS-1 Safety Analysis set who had their treatment interrupted due to AEs. The most common reasons were due to cognitive disorder (4.5%), increased creatinine/AKI (4%), pleural effusion (3.0%), dyspnea (3.0%), peripheral edema (2%), diarrhea (2%), pyrexia (2%), pneumonia (2%), and ataxia/fall/gait disturbance (2.0%).[11]

Table 31: Summary of adverse events that resulted in dose interruptions, Safety-evaluable Analysis Population – May 31, 2018 cut-off date

Preferred Term	*NTRK* Adult n=68	*ROS1* NSCLC Adult n=133	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric n=17	All n=355
Total %	56	45	43	38	46
Increased creatinine/AKI	6	4	1.5	12.5	3.9
Fatigue	7	1.5	4	6	3.7
Anemia	9	0	4	0	3.1
Diarrhea	3	2	3	6	2.8
Pyrexia	3	2	4	0	2.8
Dizziness	1.5	5	0.7	0	2.5
Nausea	4	1.5	2	0	2.3
Dyspnea	3	3	1.5	0	2.3
Pneumonia	3	2	3	6	2.3
Cognitive disorder	0	4.5	0.7	0	2.0
Neutropenia	0	0.7	1.5	6	2.0
AST increase	3	1.5	1.5	0	1.7
Pleural Effusion	1.5	3	0.7	0	1.7
Vomiting	0	1.5	3	6	1.4
ALT increase	3	1.5	0.7	0	1.4
Lipase increase	0	0.7	3	0	1.4
UTI	1.5	1.5	1.5	0	1.4
Peripheral edema	1.5	2	0	0	1.1
Ataxia/fall/gait disturbance	4	2	3	0	1.1
Confusional state/Mental Status change	1.5	0.7	3	0	1.1
Decreased appetite	1.5	0	1.5	0	1.1
Hypotension	0	0	0.7	0	1.1
Hypoxia	4	0	0	0	0.8

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

AEs leading to dose reduction are highlighted in Table 32. There were 34% of patients out of the 133 of the ROS-1 Safety Analysis set who had their dosages reduced due to AEs. The most common reasons were due to dizziness (6.0%), increased creatinine (4.0%), peripheral sensory neuropathy/parasthesia/peripheral neuropathy (4.0%), confusional state/mental status change/somnolence/depressed level of consciousness/depression/agitation/disturbance in attention (4.0%), and ataxia/fall/gait disturbance (3.0%).[11]

Table 32: Summary of adverse events that resulted in dose reductions in ≥1%, Safety-evaluable Analysis Population – May 31, 2018 cut-off date

Preferred Term	*NTRK* Adult (n=68)	ROS1 NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	41	34	16	25	28
Dizziness	4.4	6	2.2	0	3.9
Increased creatinine	6	4	0.7	6	3.1
Fatigue	6	2	0.7	0	2.3
Anemia	7	0	0.7	0	1.7
Increased weight	1.5	0.7	0.7	6	1.4
Ataxia/ Gait disturbance/balance disorder	3	3	1.5	0	1.0
Cognitive disorder	1.5	2	0	0	1.0
Peripheral sensory neuropathy/paresthesia/peripheral neuropathy	3	4	1.5	0	1.0
Gait disturbance	3	0.7	0.7	0	1.0
Arthralgia	0	1.5	1.5	0	1.0
Confusional state/mental status change/somnolence/depressed level of consciousness /depression/agitation/disturbance in attention	1.5	4	1.5	0	1.0

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

As outlined in Table 33, there were nine patients (7%) of the 133 adult ROS-1 NSCLC safety analysis set that had an AE leading to death. The most common reason for AEs leading to death included meningeal metastases (1.4%), dyspnea (0.7%), pneumonia (0.7%), sepsis/septic shock (0.7%), cardiogenic shock (0.7%), cerebral infarction (0.7%), large intestine perforation (0.7%), and pulmonary embolism (0.7%).[11]

Table 33: Summary of adverse events that resulted in death, Safety-evaluable Analysis Population – May 31, 2018 cut-off date

Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total number (%)	6 (9)	9 (7)	5 (4)	0 (0)	20 (6)
Acute Respiratory Failure	2 (3)	0 (0)	1 (0.7)	0 (0)	2 (0.6)
Cardio-respiratory Arrest	2 (3)	0 (0)	0 (0)	0 (0)	2 (0.6)
Dyspnea	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.6)
Meningeal Metastases	0 (0)	2 (1.4)	0 (0)	0 (0)	2 (0.6)
Pneumonia	1 (1.5)	1 (0.7)	0 (0)	0 (0)	2 (0.6)
Sepsis/Septic Shock	1 (1.5)	1 (0.7)	1 (0.7)	0 (0)	3 (0.9)
Cardiogenic Shock	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Cerebral Infarction	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Completed Suicide	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)
Large Intestine Perforation	0 (0)	1(0.7)	0 (0)	0 (0)	1 (0.3)
Pulmonary Embolism	0 (0)	1 (0.7)	0 (0)	0 (0)	1(0.3)
Tumor Lysis Syndrome	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)

Source: Rozlytrek (entrectinib). Multi-discipline review. U.S. Food and Drug Administration (FDA); 2019[11]

Overall Safety Populations, n = 355, Oct 31, 2018 cut-off: Results were also provided by the sponsor for the October 31, 2018 update including the 355 patients in the Overall Safety Analysis Population (Table 34). The incidence and severity of treatment related AEs was overall consistent with those seen at the May 31, 2018 data cut-off date. The three most common treatment related AEs (all grades) were dysgeusia (41.7%), fatigue (34.4%), and dizziness (25.4%). For grade ≥3 AEs, the most common were weight increased (5.6%), anemia (4.5%), and fatigue (3.1%).

Table 34: Overview of Treatment related Adverse Events (≥10%) in the Integrated Safety Population – October 31, 2018 cutoff date

n (%)	Safety evaluable population (N=355)	
	All grades	**Grade ≥3**
Dysgeusia	148 (41.7)	1 (0.3)
Fatigue	122 (34.4)	11 (3.1)
Dizziness	90 (25.4)	2 (0.6)
Constipation	85 (23.9)	1 (0.3)
Diarrhea	83 (23.4)	5 (1.4)
Nausea	75 (21.1)	0
Weight increased	73 (20.6)	20 (5.6)
Paresthesia	67 (18.9)	0
Blood creatinine increased	57 (16.1)	2 (0.6)
Myalgia	56 (15.8)	2 (0.6)
Odema peripheral	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	45 (12.7)	2 (0.6)
Aspartate aminotransferase increased	39 (11.0)	4 (1.1)*

*One Grade 4 event (increased aspartate aminotransferase) and no Grade 5 events were evaluated by investigators to be related to study treatment

Source: Sponsor's checkpoint meeting follow-up responses[28]

Safety Population, n = 210 and n = 504 – October 31, 2018 cut-off: An additional approximate five months of safety data were provided by the sponsor for 504 patients in totality, with a subset of 210 patients in the ROS-1 positive NSCLC Safety Analysis set (Table 35). Overall, the types, frequencies, and intensities of AEs reported in this safety update were consistent with the results reported in the initial safety analysis. Almost all patients in both data sets experienced AEs, with [redacted] experiencing SAEs. [redacted] of patients experienced AEs leading to discontinuation and [redacted] experienced AEs leading to death.[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 35: Overview of Adverse Events in the Integrated Safety Population – October 31, 2018 cut off

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Submission materials[3]

Treatment related adverse events

The most common treatment related adverse events of all grades for the n = 210 safety set are presented in Table 36. The incidence and severity of treatment related AEs was overall similar to those seen for the n = 134 safety set at the May 31, 2018 data cut-off date. The most common treatment related AEs were dysgeusia ([redacted]), dizziness ([redacted]), paraesthesia ([redacted]), constipation ([redacted]), diarrhoea ([redacted]), and nausea ([redacted]). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by Sponsor that it can be publicly disclosed, whichever is earlier).*

Table 36: Most Common Treatment Related Adverse Events (all Grades) (≥10%) in the ROS-1 NSCLC Safety Population (n = 210), – October 31, 2018 cut off

Source: submission materials[28]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until June 30, 2021 or until notification by Sponsor that it can be publicly disclosed, whichever is earlier).

The most common treatment related adverse events for the n = 504 safety set are presented in Table 37. The incidence and severity of treatment related AEs was overall similar to those seen for the n = 355 safety set at the May 31, 2018 data cut-off date. The top four most common treatment related AEs of all grades were dysgeusia (39.7%), fatigue (31.5%), dizziness (27.2%), and constipation (24.0%).

Table 37: Most Common Treatment Related Adverse Events (≥10%) in the Overall Integrated Safety Population (n = 504) – October 31, 2018 cut off

n (%)	Safety evaluable population (N=504)			
	All grades	Grade 3	Grade 4	Grade 5
Dysgeusia	200 (39.7)	1 (0.2)	0	0
Fatigue	159 (31.5)	14 (2.8)	0	0
Dizziness	137 (27.2)	3 (0.6)	0	0
Constipation	121 (24.0)	1 (0.2)	0	0
Diarrhea	115 (22.8)	10 (2.0)	0	0
Nausea	100 (19.8)	2 (0.4)	0	0
Weight increased	104 (20.6)	27 (5.4)	0	0
Paresthesia	88 (17.5)	0	0	0
Blood creatinine increased	88 (17.5)	2 (0.4)	0	0
Myalgia	76 (15.1)	2 (0.4)	0	0
Odema peripheral	69 (13.7)	2 (0.4)	0	0
Anemia	69 (13.7)	17 (3.4)	0	0
Vomiting	61 (12.1)	2 (0.4)	0	0
Aspartate aminotransferase increased	65 (12.9)	8 (1.6)	2 (0.4)	0
Alanine aminotransferase increased	58 (11.5)	8 (1.6)	2 (0.4)	0
Arthralgia	53 (10.5)	2 (0.4)	0	0

CCOD: Oct 31 2018. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.

Source: Submission materials[3]

6.4 Ongoing Trials

In additional to STARTRK-2 and STARTRK-NG, one other ongoing trial (phase 3 trial) of entrectinib in ROS-1 positive solid tumors was identified, which is outlined in Table 38.

Table 38: Ongoing Trials of Entrectinib in NSCLC

Trial Design	Inclusion/ Exclusion Criteria	Intervention and Comparator	Trial Outcomes
Trial: NCT04603807[9] **Characteristics:** Multicentre, randomised, open-label, phase 3 trial **Estimated enrollment:** N = 220 **Number of centres and countries:** NR **Patient Enrollment Dates:** May 3, 2016 – (ongoing) **Estimated start date:** April 30, 2021 **Estimated primary completion date:** January 31, 2027 **Estimated study completion date:** November 30, 2027 **Funding:** Hoffman-La Roche Ltd.	**Key Inclusion Criteria:** • Male or female subjects aged ≥ 18 years • Histologically or cytologically-confirmed diagnosis of advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC that harbors a documented ROS-1 gene rearrangement. • No prior treatment with a ROS-1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC • Prior radiotherapy is allowed if more than 14 days have elapsed between the end of treatment and randomization • Measurable systemic disease according to RECIST v1.1 • Participants with measurable and non-measurable CNS lesions per RECIST v1.1, including leptomeningeal carcinomatosis • Life expectancy of at least 12 weeks • ECOG PS of 0, 1 or 2 • Adequate hematologic, renal, liver functions • Participants must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment • Ability to swallow entrectinib and crizotinib intact without chewing, crushing, or opening the capsules	**Intervention:** • Entrectinib orally at a dose of 600 mg (three 200 mg capsules per day) with or without food **Comparator:** • Crizotinib orally at a dose of 250 mg twice daily with or without food	**Primary:** • PFS in patients with CNS metastases at baseline using RECIST version 1.1 assessed by BICR **Secondary:** • CNS-PFS using RECIST version 1.1 assessed by BICR • ORR including CR or PR using RECIST version 1.1 assessed by BICR • DOR using RECIST version 1.1 assessed by BICR • PFS using RECIST version 1.1 assessed by BICR • OS • EORTC QLQ-C30 • EORTC QLQ-LC13 • CNS-ORR using RECIST version 1.1 assessed by BICR • CNS-DOR using RECIST version 1.1 assessed by BICR • Safety

Trial Design	Inclusion/ Exclusion Criteria	Intervention and Comparator	Trial Outcomes
	• For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for up to 5 weeks after the last dose of entrectinib or for at least 90 days after the last dose of crizotinib • For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm. **Key Exclusion Criteria:** • Prior treatment with a ROS-1 tyrosine kinase inhibitor, chemotherapy or other systemic therapy for advanced or recurrent (Stage IIIB/C not amenable for radical treatment) or metastatic (Stage IV) NSCLC • NCI-CTCAE v5.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia, fatigue, nausea and lack of appetite), which have not shown improvement and are strictly considered to interfere with current study medication • History of recent (within the past 3 months) symptomatic congestive heart failure or ejection fraction ≤ 50% observed during screening for the study • History of prolonged QTc interval • Peripheral sensory neuropathy ≥ Grade 2 • Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis • Previous malignancy within the past 3 years • Incomplete recovery from any surgery prior to the start of study treatment • Active GI disease (e.g., Crohn's disease, ulcerative colitis or short gut syndrome) or other		

Trial Design	Inclusion/ Exclusion Criteria	Intervention and Comparator	Trial Outcomes
	malabsorption syndrome that would reasonably impact drug absorption • History of prior therapy-induced pneumonitis • Any condition (in the past 3 months) e.g., myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, or uncontrolled arrhythmias requiring medication • Known active infections (bacterial, fungal or viral, including human immunodeficiency virus positive) • History of hypersensitivity to any of the additives in the entrectinib and/or crizotinib drug formulations • Pregnant or lactating women • Known HIV positivity or AIDS-related illness • Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications.		
Trial: STARTRK-NG STARTRK-Next Generation RXDX-101-03 NCT02650401 **Characteristics:** Multicentre, non-randomised, open-label, phase 1/2 dose escalation study **N [total** = 16 (enrolled and treated phase 1 dose escalation only) **N [ROS-1 positive]** = 0 **N [Integrated Analysis]** = 0 (efficacy analysis); 0 (safety analysis); 0	**Key Inclusion Criteria:** • Male or female subjects from birth to 18 years of age, unless enrolled in Part E • BSA of ≥0.45 m^2 at the time of study enrollment, unless enrolled in Part E • Patients had to have measurable or evaluable disease as per RECIST 1.1 ± Curie Scale Criteria or RANO/RANO-BM • Tumour type: 1) Part A: relapsed or refractory extracranial solid tumours and (Phase 1b expansion) relapsed or refractory extracranial solid tumours with molecular alterations, non-gene fusions; 2) Part B: relapsed or refractory primary CNS tumours with molecular alterations, including gene fusions, documented by a CLIA-approved lab prior to enrolment; 3) Part C: relapsed or refractory neuroblastoma; 4) Part D:	**Phase 1:** • Entrectinib monotherapy orally at a starting dose of 250 mg/m^2 (~63% of adult BSA-based RP2D of 400 mg/m^2) with additional dose levels: 400 mg/m^2; 550 mg/m^2; and 750 mg/m^2 • Administered QD for 28 consecutive days (4-week repeated cycles) **Phase 2:** • RP2D determined to be 550 mg/m^2, orally, applicable to Parts B-D	**Primary:** • MTD or RP2D • ORR **Secondary:** • Safety • PK • DOR, TTR, CBR, PFS, OS in all enrolled patients (Part A, C, D) receiving RP2D using RECIST 1.1 ± Currie Scale • Intracranial tumour response, DOR, TTR, CBR, CNS-PFS in Parts B and D receiving entrectinib at RP2D and presenting with measurable primary or secondary CNS disease at

Trial Design	Inclusion/ Exclusion Criteria	Intervention and Comparator	Trial Outcomes
Number of centres and countries: 35 sites in the US **Patient Enrollment Dates:** May 3, 2016 – (ongoing) **Data cut-off (DCO) for integrated analysis:** May 31, 2018 (primary analysis) **Date of enrollment cut-off for integrated analysis:** November 30, 2017 **End of data collection/data available:** Quarter 1, 2029 **Funding:** Hoffman-La Roche Ltd.	relapsed or refractory non-neuroblastoma, extracranial solid tumours with NTRK1/2/3, ROS-1, or ALK gene fusions documented by a CLIA-approved lab prior to enrolment; 5) Part E: any patient unable to swallow capsules who otherwise meet all other eligibility criteria for Part A (expansion) B, C or D • Histologic/molecular diagnosis of malignancy at diagnosis or the time of relapse • Archival tumour tissue from diagnosis or, preferably, at relapse • Performance status: Lansky or Karnofsky score ≥60% • Minimum life expectancy of at least 4 weeks • No curative first-line treatment option for patient's cancer or recurrent/refractory solid tumours and primary CNS tumours • Adequate organ and neurologic function **Key Exclusion Criteria:** • Receiving other experimental therapy • Known congenital long QT syndrome • Known active infections • EIAEDs within 14 days of first dose • Prior treatment with TRK, ROS-1, or ALK inhibitors • Neuroblastoma bone marrow space-only disease • Incomplete recovery from acute effects of any surgery prior to treatment • Active GI disease or malabsorption syndromes	• Part E: alternative dosing methods at one dose level de-escalated from the RP2D for patients unable to swallow, patients ≤2 years of age eligible only for Part E • Part E: Nasogastric/gastric tube as an alternative to soft food/liquid option and dose recommendations for those with BSA < 0.43 m^2 are 250 mg/m^2 if 1 – 6 months old and 100 mg/m^2 if newborn – 1 month	baseline using RANO or RANO-BM as applicable • Growth (height and weight); puberty (Tanner); neurological function, neurocognitive function • ORR in all patients with NTRK 1/2/3 gene fusions regardless of phase or cohort using RANO for CNS and RECIST 1.1 for extracranial tumours assessed by BICR • Palatability and tolerability of age-appropriate formulation **Exploratory** • Molecular mechanisms of resistance to entrectinib • Clinicopathologic differences and response to entrectinib in various tumour types harboring gene arrangements under investigation

7 Supplemental Questions

The following supplemental questions were identified during development of the review protocol as relevant to the CADTH review of entrectinib for NSCLC:

- Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison Using Matched Adjusted Indirect Comparison
- Critical Appraisal of the Sponsor-Submitted Propensity Score Analysis Using Real-World Data

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed

7.1 Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison Using Matched Adjusted Indirect Comparison

7.1.1 Objective

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor provided indirect treatment comparisons (ITCs) using matched adjusted indirect comparisons (MAICs) of the relevant comparators, which were identified based on a systematic review of treatments for NSCLC.[35] The objective of the MAICs was to estimate the relative treatment effects of entrectinib compared with the following: 1) crizotinib (based on the PROFILE 1001 study [36] and pooled PROFILE 1001/Wu 2018[37] studies—for the PFS outcome only), 2) pemetrexed plus platinum followed by pemetrexed maintenance (based on the ASCEND-4 study[38]), and 3) chemotherapy (based on the PROFILE 1007 study[39]) for patients with advanced or metastatic ROS-1 NSCLC in the first- or second-line setting.[35] Results of the MAICs were subsequently incorporated into the PE model to help inform cost-effectiveness estimates for entrectinib.

7.1.2 Findings

The sponsor submitted multiple MAICs, which have been described and critically appraised in the sections below.

Methods

Systematic review

The systematic review that was submitted by the sponsor was conducted to identify data on relevant comparators included in the ITC. The review was based on searches of multiple bibliographic databases via the OVID platform (from inception until March 31, 2020), reference lists of eligible studies and relevant reviews, conference proceedings over the past three years, HTA agencies, clinical trial registries, cost effectiveness databases, and Google Scholar.

The eligibility criteria for the systematic review were adults aged over 18 years with locally advanced or metastatic NSCLC (Stage IIIb/IV) that were ROS-1 fusion-positive. Randomized controlled trials (RCTs), non-randomized comparative trials, single-arm trials, and prospective/retrospective observational studies were included if they included more than five patients. The intervention of interest was entrectinib. The comparators were first-line treatments (crizotinib or pemetrexed plus platinum-based chemotherapy) or second-line treatments (pemetrexed or docetaxel). Studies containing one of the interventions of interest among at least one study arm were considered for inclusion regardless of whether a comparator was present or not (i.e., single-arm studies without a comparator were eligible). Studies investigating other types of treatments that were not considered first-line or second-line therapy for NSCLC (e.g., pharmacotherapy, radiotherapy, chemoradiotherapy, and adjuvant or neoadjuvant therapy) were excluded. The language of inclusion was not restricted. The inclusion criteria are outlined in Table 39.

Table 39: PICOS Eligibility Criteria

PICOS Item	Eligibility Criteria
Population	Adults aged over 18 years with locally advanced or metastatic NSCLC (Stage IIIb/IV) that are ROS-1 fusion-positive
Intervention	Entrectinib
Comparators	First-line: • Crizotinib • Pemetrexed + platinum-based chemotherapy Second-line: • Pemetrexed • Docetaxel
Outcomes	Efficacy outcomes: • Objective response rate • Duration of response • Time to response • Clinical benefit rate • CNS-progression-free survival • Overall survival • Progression-free survival • Intracranial tumour response • Response rates (complete response, partial response, stable disease) Harms outcomes: • All-grade treatment related adverse events • Treatment-related grade 3 or 4 adverse events • Treatment-related serious adverse events • Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to adverse events) • Mortality All health-related quality of life and patient reported outcomes captured in the studies
Study design	Randomized controlled trials, non-randomized comparative trials, single-arm trials, and prospective/retrospective observational studies (only if they included more than 5 patients)

Source: pCODR Submission[35]

Regarding the conduct of the systematic review, both title/abstract and full-text article levels of screening were conducted by a single reviewer, which was independently checked by a second reviewer with discrepancies resolved by consensus. Data were abstracted by a single reviewer and all data inputs were independently checked against the source document by a second reviewer. During the data abstraction, no calculations to obtain additional data were performed (for example, if a percentage was provided, they did not back calculate the numerator and denominator).[35] Quality assessment of the included single arm trials and observational studies was performed using the Downs and Black checklist[40]; whereas RCTs were assessed using the NICE checklist.[41]

Methods for indirect treatment comparisons

As noted above, a series of ITCs were conducted versus entrectinib (based on the integrated analysis from the sponsor with the May 1, 2019 cut-off [integrated analysis of ALKA, STARTRK-1, and STARTRK-2[3]]), as follows:

1) Crizotinib (based on the PROFILE 1001 study[36] and pooled PROFILE 1001/Wu[14] 2018 studies[37]—for the PFS outcome only),

2) Pemetrexed plus platinum followed by pemetrexed maintenance (based on the ASCEND-4 study[38]), and

3) Chemotherapy including docetaxel monotherapy or pemetrexed monotherapy (based on the PROFILE 1007 study[39]).

In order to conduct the ITCs that are mentioned above in 1-3,[35] the sponsor selected the unanchored MAIC approach, as the evidence base identified through the systematic review did not directly compare the intervention with any of the eligible comparators via RCTs or non-randomized controlled studies. Individual patient data (IPD) was available for entrectinib using data from the integrated analysis and summary level data was available for the comparators. A common comparator was not available to conduct an anchored MAIC, as all of the studies included in the analysis were either single-arm trials or included comparators that were not eligible. A naïve indirect comparison was not selected, as the sponsor noted this analysis compares study groups from different trials as if they were from the same RCT; accordingly, the comparisons are susceptible to bias.[35] For one outcome (PFS) in the comparison with crizotinib, a MAIC using the entrectinib integrated analysis and pooled PROFILE 1001 (2019) & Wu (2018) crizotinib data was conducted.[37]

For the OS and PFS outcomes, weighted Kaplan Meier curves were generated based on the IPD from the integrated analysis for the entrectinib trials using the May 1, 2019 data cut-off date.[35] IPD were not available for the comparators. As such, pseudo-IPD were recreated by digitizing the existing Kaplan Meier curves using the GetData software[42] for the comparators. Hazard ratios and 95% CIs were estimated using weighted Cox proportional hazards models for OS and PFS; whereas, odds ratios and 95% CIs were calculated for ORR and treatment discontinuation due to AEs. In the sponsor's response, they noted that log-log plots and Schoenfeld tests were conducted to test the proportional hazards assumptions for the OS and PFS outcomes.[28]

The estimates used in the MAIC were derived using propensity score weighting to adjust for the following patient characteristics (whenever available): age, disease stage (Stage IIIB, Stage IV with CNS metastasis, Stage IV with non-CNS metastasis), sex, smoking status (current, former, never), ECOG PS (0, 1, 2), histology (adenocarcinoma, non-adenocarcinoma), number of prior anti-cancer therapies (0, ≥1), and CNS metastasis. These variables were sources of heterogeneity that the sponsor wished to consider in the MAICs. The sponsor noted that these variables were identified through a literature search and expert medical opinion.[28] The sponsor noted that when estimates are made by weighting a sample, the effective sample size is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate and that weighting always reduces the effective sample size. Using logistic regression, a propensity score was estimated to determine the odds of being enrolled into a comparative source of evidence. Using this method, one set of propensity weights was derived for each comparative study. Scaled weights were used to improve the balance in baseline characteristics between the index study (the study with IPD) and the comparator study for those characteristics included in the weighting procedure. A bootstrap estimator was used to account for a within-subject correlation in outcomes, which also provided an estimate of sampling uncertainty. The bootstrapping method included the following steps: 1) patients treated with entrectinib were sampled with replacement and this was called the bootstrap dataset, 2) for each bootstrap dataset, a set of weights was derived as per above, 3) for each bootstrap dataset and corresponding set of weights, a HR was obtained. This was repeated 1,000 times to obtain a distribution of HRs with 2.5 and 97.5 percentiles used to generate confidence intervals for the OS and PFS outcomes.[35]

Results

Systematic review results and NMA feasibility assessment

Forty-one studies reported in 54 publications were relevant and included in the systematic review.[35] The included studies examined the following interventions: entrectinib (n = 3 studies); crizotinib (n = 29 studies); pemetrexed plus platinum-based chemotherapy (n = 3 studies); crizotinib versus entrectinib, crizotinib versus platinum-based chemotherapy, and crizotinib versus platinum-pemetrexed chemotherapy (n = 3 studies, one for each of those comparisons), and three were mixed therapies. For each intervention, a source of evidence was selected to include in each of the MAICs that were conducted with the following reasons provided by the sponsor:[35]

- INDEX DATA for entrectinib: The evidence source for entrectinib was based on the integrated analysis from the sponsor with the May 1, 2019 cut-off (integrated analysis of ALKA, STARTRK-1, and STARTRK-2).[3] This was the index dataset that included the IPD for all MAICs.
- MAIC for entrectinib versus crizotinib: Studies were excluded from the MAIC because the study was reported as an abstract only, had a small sample size, had heterogeneity in the treatment received, and had insufficient reporting of outcome data. Based on this, it was deemed that the most appropriate study was PROFILE 1001, which reported both OS and PFS. For PFS, data was pooled from PROFILE 1001 with Wu 2018;[14] this was conducted to align with the evidence considered in the recent pCODR review of crizotinib in ROS-1 positive NSCLC[43]. Wu 2018 did not include data on OS so this outcome was not included; therefore, OS comparisons did not include the pooling of PROFILE 1001 and Wu 2018 (i.e. focused on PROFILE 1001 only).

- MAIC for entrectinib versus pemetrexed plus platinum and pemetrexed maintenance: Studies were excluded because they did not include pemetrexed maintenance therapy or allowed patients to receive a TKI treatment before or after pemetrexed treatment. Based on this, it was deemed that the most appropriate study was ASCEND-4.[38]
- MAIC for entrectinib versus chemotherapy (docetaxel monotherapy or pemetrexed monotherapy): Studies were excluded because patients received one or two prior lines of therapy or had progressed on or were intolerant to crizotinib. Based on this, it was deemed that the most appropriate study was PROFILE 1007.

In summary, the following studies were included across all of the MAICs that were conducted entrectinib integrated analysis,[3] PROFILE 1001,[36] ASCEND-4,[38] PROFILE 1007,[39] and Wu 2018.[14]

Trial characteristics

The detailed inclusion criteria for the studies included in the multiple MAICs were not specifically reported. Instead, a summary of the trial inclusion criteria was provided,[35] which are outlined in Table 40. Data for entrectinib came from pooling data across three single-arm trials (ALKA, STARTRK-1, and STARTRK-2). PROFILE 1001 provided data on crizotinib through a single-arm trial. Wu 2018 was a single arm trial providing data on crizotinib. ASCEND-4 was a randomized trial that compared ceritinib to pemetrexed plus platinum-based chemotherapy followed by pemetrexed maintenance. Although ASCEND-4 was a randomized trial, only the pemetrexed plus platinum-based chemotherapy followed by pemetrexed maintenance group was included in the MAIC. PROFILE 1007 was a randomized trial that compared crizotinib to docetaxel monotherapy or pemetrexed monotherapy. Although PROFILE 1007 was a randomized trial, only the docetaxel monotherapy or pemetrexed monotherapy group was included in the MAIC.

The age of participants was reported as being adults aged 18 years and older for the entrectinib integrated analysis,[3] Wu 2018, and ASCEND-4 trial;[38] it was not reported for PROFILE 1001[36] or PROFILE 1007[44]. The patient population was advanced or metastatic ROS-1 in the entrectinib integrated analysis,[3] Wu 2018, and PROFILE 1001[36] trial. In contrast, the patient population was advanced or metastatic anaplastic lymphoma kinase positive (ALK) for PROFILE 1007[39] and non-squamous advanced metastatic ALK in the ASCEND-4 trial[38]. Prior treatments were allowed for the entrectinib integrated analysis[3] and PROFILE 1001[36] and Wu 2018 studies; however, treatment was not permitted for the ASCEND-4 trial[38] and only one prior platinum-based chemotherapy was allowed for PROFILE 1007[39]. Stable brain metastases were allowed in all trials, yet this was unclearly reported for PROFILE 1001.[36] Crossover to ceritinib occurred for 43% of patients in the ASCEND-4 trial and 64% of patients in the PROFILE 1007[39] trial crossed over to crizotinib.

Baseline patient characteristics for the groups that were selected for inclusion in the multiple MAIC analyses are summarized in Table 41. The median duration of follow-up was 20.9 months for the integrated analysis,[3] 16.4 months for PROFILE 1001[36], 21.4 months for Wu 2018,[14] 12.1 months for PROFILE 1007,[39] and not reported for ASCEND-4.[38] The sample size across the included arms in the MAICs ranged from 53 patients administered crizotinib in the PROFILE 1001 trial to 187 patients administered pemetrexed plus platinum and pemetrexed maintenance therapy in ASCEND-4. The median age ranged from 49 to 55 years and the percentage of female patients ranged from 55% in the PROFILE 1007 trial to 64% in the pooled entrectinib studies. The proportion of patients who never smoked ranged from 60% in the pooled entrectinib studies to 76% in PROFILE 1001. The stage IV CNS disease stage ranged from 18% in the pooled PROFILE 1001 and Wu 2018 data to 43% in the pooled entrectinib studies. Adenocarcinoma ranged from 94% in PROFILE 1007 to 98% in ASCEND-4 (pemetrexed plus platinum and pemetrexed maintenance therapy arm). Patients with ECOG PS 2 ranged from 0.6 % in Wu 2018 to 11.7% in the pooled entrectinib studies. The following baseline characteristics were included in the estimation of the MAIC weights for comparison of entrectinib versus the pooled PROFILE 1001 and Wu 2018 data: the median age in years was 52.5, 72.8% never smoked, 0.6% were in ECOG PS 2, 97.2% had adenocarcinoma, 17.2% were treatment naïve, 57.2% were female, and 18.1% had stage IV CNS.[37]

Table 40: Inclusion Criteria for the Studies Included in the Matching Adjusted Indirect Comparisons

Arm [Study design]	Treatment	Age in yrs	Performance status	Population	Prior treatment	Brain metastasis
Entrectinib integrated analysis [results pooled across 3 single-arm trials]	Entrectinib 600 mg daily	≥18	ECOG: 0, 1, 2	ROS-1 positive advanced/metastatic	Prior anticancer treatment allowed	Stable brain metastases allowed
PROFILE 1001 [single arm trial]	Crizotinib 250 mg twice daily (starting dose)	NR	ECOG: 0, 1, 2	ROS-1 positive advanced	Any number of prior treatments	NR
Wu 2018 [single arm trial]	Crizotinib, 250 mg twice daily (starting dose)	≥18	ECOG: 0, 1	ROS-1 positive advanced/metastatic	Three or fewer lines of prior systemic therapies for advanced stage disease	Stable brain metastases allowed
ASCEND-4 [randomized trial]	Ceritinib	≥18	WHO: 0, 1, 2	ALK+ advanced/metastatic (non-squamous)	Treatment naïve	Stable brain metastases allowed
	Pemetrexed plus platinum and pemetrexed maintenance (pemetrexed: 500 mg/m^2 every 3 weeks)	≥18	WHO: 0, 1, 2	ALK+ advanced/metastatic (non-squamous)	Treatment naïve	Stable brain metastases allowed
PROFILE 1007 [randomized trial]	Crizotinib, 250 mg twice daily	NR	ECOG: 0, 1, 2	ALK+ advanced/metastatic	One prior platinum-based chemotherapy regimen	Stable brain metastases allowed
	Docetaxel monotherapy (75 mg/m^2 every 3 weeks) or pemetrexed monotherapy (500 mg/m^2 every 3 weeks)	NR	ECOG: 0, 1, 2	ALK+ advanced/metastatic	One prior platinum-based chemotherapy regimen	Stable brain metastases allowed

b.i.d. = twice daily; Gy = grays; HCC = hepatocellular carcinoma; IQR = interquartile range; MBq = megabecquerel; NR = not reported; SD = standard deviation; SIRT = selective internal radiotherapy.

Source: pCODR Submission[35]

Table 41: Baseline Patient Characteristics for the Arms Included in the Matching Adjusted Indirect Comparisons

Arm, median duration of follow-up	Treatment, Sample size	Median age in yrs, range	% Female	Smoking status %	Disease stage %	Adenocarcinoma %	ECOG Status %
Integrated analysis, 20.9 months	Entrectinib, 94	53, 27-86	63.8	Never: 59.6 Former: 89.5 Current: 10.5	Stage IIIB: 1.1 Stage IV (CNS): 42.6	95.7	0: 37.2 1: 51.1 2: 11.7
PROFILE 1001,[36] 16.4 months	Crizotinib, 53	55, 25-81	56.6	Never: 75.5 Former: 24.5 Current: 0	NR	96.2	0: 43.4 1: 54.7 2: 1.9
Wu 2018,[14] 21.4 months	Crizotinib, 127	52.5, 23-80	57.2	Never: 72.8 Current: 28.3	Stage IV CNS: 18.1	97.2	0: 26.8 1: 73.2 2: 0.6
ASCEND-4, NR	Pemetrexed plus platinum and pemetrexed maintenance, 187	54, 22-80	61.0	Never: 65.2 Former: 26.7 Current: 8.0	Stage IIIB: 2.7 Stage IV (Non-CNS): 64.2 Stage IV (CNS): 33.2	98.0	0: 37.4 1: 56.2 2: 5.9
PROFILE 1007,[39] 12.1 months	Docetaxel monotherapy or pemetrexed monotherapy. 174	49, 24-85	55.2	Never: 63.8 Former: 31.0 Current: 5.2	Stage IIIB: 9.2 Stage IV (Non-CNS): 56.3 Stage IV (CNS): 34.5	94.3	0: 37.4 1: 54.6 2: 8.1

b.i.d. = twice daily; Gy = grays; HCC = hepatocellular carcinoma; IQR = interquartile range; MBq = megabecquerel; NR = not reported; SD = standard deviation; SIRT = selective internal radiotherapy.

Source: pCODR Submission[35]

Assessment of Homogeneity

The sponsor assessed for clinical heterogeneity across the MAICs for the comparators versus the entrectinib integrated analysis that included the IPD for the MAIC. To assess heterogeneity, the following variables were compared across the studies: age, disease stage, sex, smoking status, ECOG PS, histology, number of prior anti-cancer therapies, CNS metastasis, and treatment switching. The sponsor noted that the median age was consistent across the trials. Regarding disease stage, all studies included patients with locally advanced or metastatic disease and the proportion of patients with CNS metastasis was a subset of those with metastatic/stage IV disease. It was noted that the assumption that CNS metastasis and non-CNS metastasis were mutually exclusive could not be confirmed as this was based on aggregate data only. For CNS metastases at baseline, this information was not reported for PROFILE 1001. For the studies reporting this data, CNS metastases at baseline was higher for the entrectinib integrated analysis (42.6%)[35] compared with ASCEND-4 (33.2%), PROFILE 1007 (34.5%), and Wu 2018 (18.1%). The percentage of female patients varied across the studies, with the entrectinib integrated analysis including the greatest proportion of female patients (63.8%), followed by ASCEND-4 (61.0%), Wu 2018 (57.2%), PROFILE 1001 (56.6%), and PROFILE 1007 (55.2%). For smoking status, the entrectinib integrated analysis had the lowest proportion of patients who never smoked (59.6%) compared to PROFILE 1001 (75.5%), Wu et al. 2018[14] (72.9%), ASCEND-4 (65.2%), and PROFILE 1007 (63.8%).[35] Furthermore, the entrectinib integrated analysis had more current smokers (10.5%) compared with ASCEND-4 (8.0%), PROFILE 1007 (5.2%), and PROFILE 1001 (0), yet fewer current smokers than Wu et al. 2018 (28.3%). For the percentage of patients with adenocarcinoma, ASCEND-4 had the highest number of patients (98.0%), followed by Wu et al. 2018[14] (97.2%), PROFILE 1001 (96.2%), entrectinib integrated analysis (95.7%), and PROFILE 1007 (94.3%). The sponsor noted heterogeneity regarding ECOG PS, with the entrectinib integrated analysis reporting more patients with a performance status of 2 (11.7%) compared with PROFILE 1007 (8.1%), ASCEND-4 (5.9%), PROFILE 1001 (1.9%), and Wu 2018 (0.6%). It was mentioned that an inclusion of a higher proportion of patients with ECOG 2 in the entrectinib studies may reflect a patient population with more advanced disease compared to the others. The sponsor noted heterogeneity in the prior anti-cancer treatment that patients were exposed to. The entrectinib integrated analysis, PROFILE 1001, PROFILE 1007, and Wu 2018 included a mixture of patients who were treatment-naïve or received previous anti-cancer treatment. In contrast, ASCEND-4 only included treatment-naïve patients. In both PROFILE 1001 and Wu 2018, more than 80% of patients received crizotinib, implying that a MAIC including these populations would largely represent patients treated at second-line or above. Another area for potential heterogeneity was treatment switching, which occurred in 43% of ASCEND-4 patients and 64% of patients in PROFILE 1007. Cross-over adjusted results were not available for either of these studies.[35]

Critical Appraisal

The risk of bias was appraised using the Downs and Black quality appraisal checklist[40], with each of the 27 items scored as yes (1 point), no (0 points), or unclear (0 points). PROFILE 1001 and Wu 2018 scored 18 points out of 27. Points were lost for lack of randomization, lack of blinding, and not reporting loss to follow up. For the ASCEND-4[28] RCT, the quality was assessed using the NICE checklist. Points were lost for lack of blinding and it was unclear whether an intention to treat analysis was performed. For the PROFILE 1007 RCT,[28] the NICE checklist was used, and points were lost for unclear randomization, lack of allocation concealment, and lack of similarity in prognostic factors at baseline. However, no risk of bias or quality assessment was provided for the entrectinib integrated analysis.

Outcomes

A summary of the outcome data reported is provided in Table 42. All trials reported the following: PFS, ORR, and grade 3+ AEs. All trials, other than Wu 2018, also reported on OS and treatment discontinuation due to AEs. None reported on any SAE, other than Wu 2018. For OS, Kaplan Meier curves were available for all comparator trials. The definitions of investigator assessed PFS varied across the comparator trials. For PROFILE 1001, it was defined as the time from administration of the first dose of crizotinib to objective disease progression or death from any cause according to the RECIST criteria. For PFS according to BICR, the definition and estimates were not reported in PROFILE 1001. For ASCEND-4, the definition was the time from randomisation to the date of the first radiologically documented disease progression (assessed by the BICR according to RECIST version 1.1) or death due to any cause. For PROFILE 1007, the definition was the time from randomisation to progression of the disease, as assessed by means of independent radiologic review (RECIST version 1.1) or to death. For ORR, the outcome was defined based on the best overall response from investigator assessment using RECIST version 1.0 in the PROFILE 1001 trial. In ASCEND-4, the definition was not reported. In PROFILE 1007 for the chemotherapy arm, the definition was tumour response via RECIST version 1.1 and confirmed by independent radiological review.[35]

Table 42: Outcomes Reported and Outcome Definitions for the Arms Included in the Matching Adjusted Indirect Comparisons

Arm	Overall Survival	Progression- Free Survival	Objective Response Rate	Any Adverse Event Grade 3+	Treatment Discontinuation due to Adverse Events
Entrectinib integrated analysis[3]	Reported Kaplan Meier curve available	Reported Defined as number of months from first dose of entrectinib to first documentation of radiographic PD as per RECIST version 1.1 or death due to any cause	Reported BICR-determined according to RECIST version 1.1	Reported	Reported
PROFILE 1001	Reported Kaplan Meier curve available	Reported Defined as defined as time from administration of the first dose of crizotinib to objective disease progression or death from any cause, RECIST defined	Reported Based on independent radiological review Best overall response was derived from investigator assessment using RECIST version 1.0	Reported	Reported
Wu 2018	Not Reported	Reported RECIST version 1.1–defined progression by independent radiology review	Reported RECIST version 1.1–defined progression by independent radiology review	Reported	Not reported
ASCEND-4	Reported Kaplan Meier curve available	Reported Defined as time from randomisation to the date of the first radiologically documented disease progression (assessed by the blinded independent review committee according to RECIST	Not Reported	Reported	Not reported

Arm	Overall Survival	Progression- Free Survival	Objective Response Rate	Any Adverse Event Grade 3+	Treatment Discontinuation due to Adverse Events
		version 1.1) or death due to any cause			
PROFILE 1007	Reported Kaplan Meier curve available	Reported Defined as time from randomisation to progression of the disease, as assessed by means of independent radiologic review (RECIST version 1.1), or to death	Reported Tumour responses were assessed via RECIST, version 1.1, and were confirmed by independent radiological review	Reported	Reported

Source: pCODR Submission[35]

Table 43: Baseline Characteristics Included in Estimation of MAIC Weights for Entrectinib Versus Crizotinib – Based on PROFILE 1001

Arm	Effective sample size	Age, years	% Never smoked	% ECOG 2	% Adeno-carcinoma	% Treatment naïve	% Female	% Stage IV CNS
Efficacy Scenario 1								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	18.1
Entrectinib	94	53.5	59.6	11.7	95.7	33.0	63.8	42.6
Entrectinib re-weighted	(53.9)	55.0	75.5	1.9	96.2	13.2	56.6	18.1
Efficacy Scenario 2								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	24.6
Entrectinib	94	53.5	59.6	11.7	95.7	33.0	63.8	42.6
Entrectinib re-weighted	(57.2)	55.0	75.5	1.9	96.2	13.2	56.6	24.6
Efficacy Scenario 3								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	42.6
Entrectinib	94	53.5	59.6	11.7	95.7	33.0	63.8	42.6
Entrectinib re-weighted	(56.2)	55.0	75.5	1.9	96.2	13.2	56.6	42.6

Arm	Effective sample size	Age, years	% Never smoked	% ECOG 2	% Adeno-carcinoma	% Treatment naïve	% Female	% Stage IV CNS
Safety Scenario 1								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	18.1
Entrectinib	209	54.9	62.2	8.6	97.1	23.0	61.7	41.1
Entrectinib re-weighted	(136.3)	55.0	75.5	1.9	96.2	13.2	56.6	18.1
Safety Scenario 2								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	24.6
Entrectinib	209	54.9	62.2	8.6	97.1	23.0	61.7	41.1
Entrectinib re-weighted	(150)	55.0	75.5	1.9	96.2	13.2	56.6	24.6
Safety Scenario 3								
Crizotinib	53	55.0	75.5	1.9	96.2	13.2	56.6	41.1
Entrectinib	209	54.9	62.2	8.6	97.1	23.0	61.7	41.1
Entrectinib re-weighted	(167.3)	55.0	75.5	1.9	96.2	13.2	56.6	41.1

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.

Note: Age is mean for entrectinib, median for crizotinib.

Source: pCODR Submission[35]

Results of MAIC

MAIC for Entrectinib versus Crizotinib

Eight variables were attempted for matching in the MAICs (age, sex, smoking status, ECOG PS, disease stage, prior anti-cancer therapy, CNS metastases, and histology). Of these, the sponsor was able to match the entrectinib integrated analysis with the PROFILE 1001 trial on the following seven variables: prior treatment, smoking status, age, sex, ECOG PS, CNS metastasis, and histology. CNS metastases was not reported in the PROFILE 1001 trial. As such, three different scenarios were considered based on different estimates from the literature: Scenario 1—CNS metastasis of 18.1% (as per Wu 2018), Scenario 2—CNS metastasis of 24.6% (as per the Flatiron trial described in Section 7.3), and CNS metastasis of 42.6% and 41.1% for the efficacy and safety analyses, respectively (as per the entrectinib integrated analysis). For scenario 1, the effective sample size for the pooled entrectinib studies was reduced by 43% from 94 patients to 54 in the efficacy analysis and by 35% from 209 to 136 for the safety analysis. For scenario 2, the effective sample size was reduced by 39% from 94 to 57 in the efficacy analysis, and by 28% from 209 to 150 patients in the safety analysis. For scenario 3, the effective sample size was reduced by 40% from 94 to 56 in the efficacy analysis and by 20% from 209 to 167 patients in the safety analysis. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment, which is presented in Table 43.

The results for the MAIC comparison of entrectinib versus crizotinib using data from PROFILE 1001 are presented in Table 44. For OS, neither entrectinib nor crizotinib was favoured based on the uncertainty reflected in the 95% CI (scenario 1: HR: 0.71, 95% CI: 0.39 to 1.11; scenario 2: 0.77, 95% CI: 0.43, 1.18, scenario 3: 0.96, 95% CI: 0.50, 1.41). The Kaplan Meier curves for OS are presented in Figure 5 to Figure 7. For PFS, neither entrectinib nor crizotinib was favoured based on the uncertainty reflected in the 95% CI (scenario 1, investigator assessment: 1.44, 95% CI: 1.07, 1.91; scenario 2, investigator assessment: 1.51, 95% CI: 1.13, 1.98; scenario 3, investigator assessment: 1.73, 95% CI: 1.30, 2.21; scenario 1, BICR: 1.07, 95% CI 0.72, 1.48; scenario 2, BICR: 1.11, 95% CI: 0.75, 1.53; scenario 3, BICR: 1.25, 95% CI: 0.79, 1.70). The Kaplan Meier curves for PFS are presented in Figure 8 to Figure 13. For the ORR, neither entrectinib nor crizotinib was favoured based on the uncertainty reflected in the 95% CI (scenario 1: 1.20, 95% CI: 0.70, 2.50, scenario 2: 1.10, 95% CI: 0.70, 2.30, scenario 3: 1.00, 95% CI: 0.60, 2.10). For discontinuation due to AEs, neither entrectinib nor crizotinib was favoured based on the uncertainty reflected in the 95% CI (scenario 1: 0.70, 95% CI: 0.30, 1.30, scenario 2: 0.70, 95% CI: 0.30, 1.30, scenario 3: 0.70, 95% CI: 0.30, 1.10).

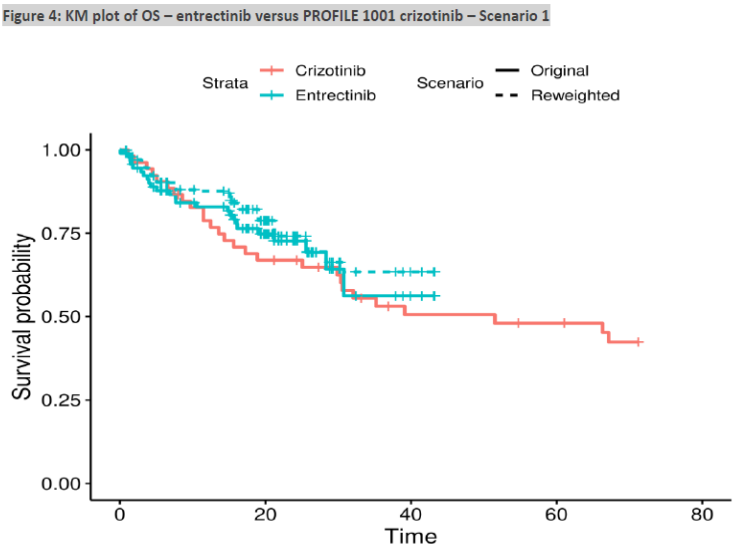
Table 44: MAIC Results for Entrectinib Against Crizotinib - Based on PROFILE 1001

Outcome	Scenario 1	Scenario 2	Scenario 3
OS, HR (95% CI)	0.71 (0.39, 1.11)	0.77 (0.43, 1.18)	0.96 (0.50, 1.41)
PFS-IA, HR (95% CI)	1.44 (1.07, 1.91)	1.51 (1.13, 1.98)	1.73 (1.30, 2.21)
PFS-BICR, HR (95% CI)	1.07 (0.72, 1.48)	1.11 (0.75, 1.53)	1.25 (0.79, 1.70)
ORR, OR (95% CI)	1.20 (0.70, 2.50)	1.10 (0.70, 2.30)	1.00 (0.60, 2.10)
Treatment discontinuation due to AE, OR (95% CI)	0.70 (0.30, 1.30)	0.70 (0.30, 1.30)	0.70 (0.30, 1.10)

AE = adverse events; BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IA = independent assessment; OR = odds ratio; ORR = objective response rate; OS = overall survival.

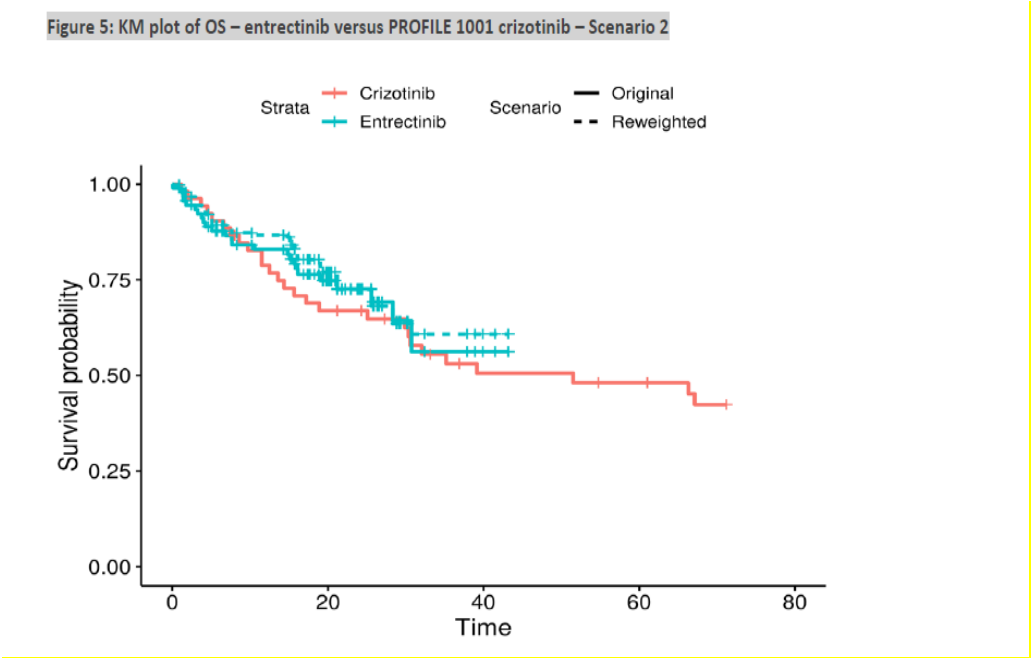
Source: pCODR Submission[35]

Figure 5: Kaplan Meier Plot for Overall Survival: Scenario 1



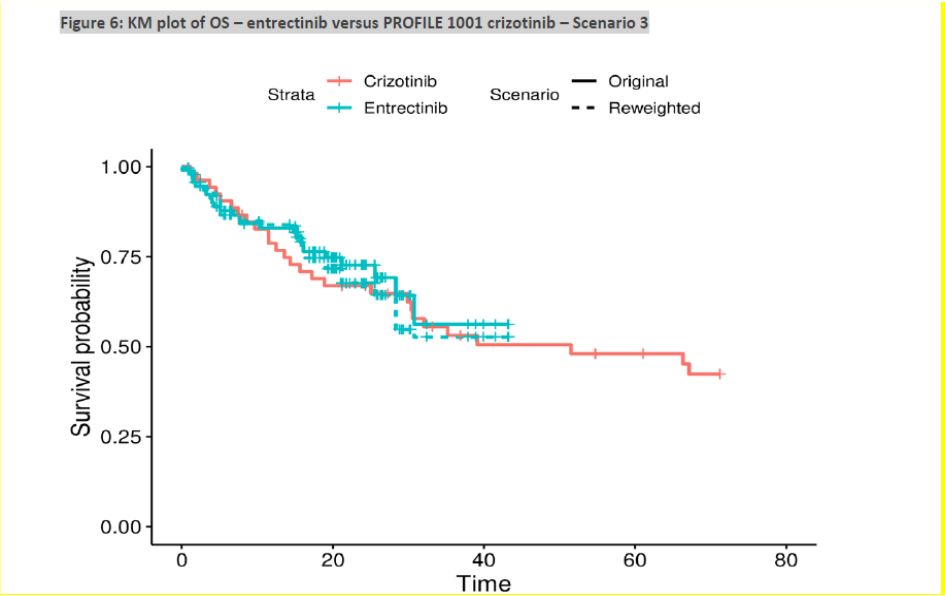
Source: pCODR Submission[35]

Figure 6: Kaplan Meier Plot for Overall Survival: Scenario 2



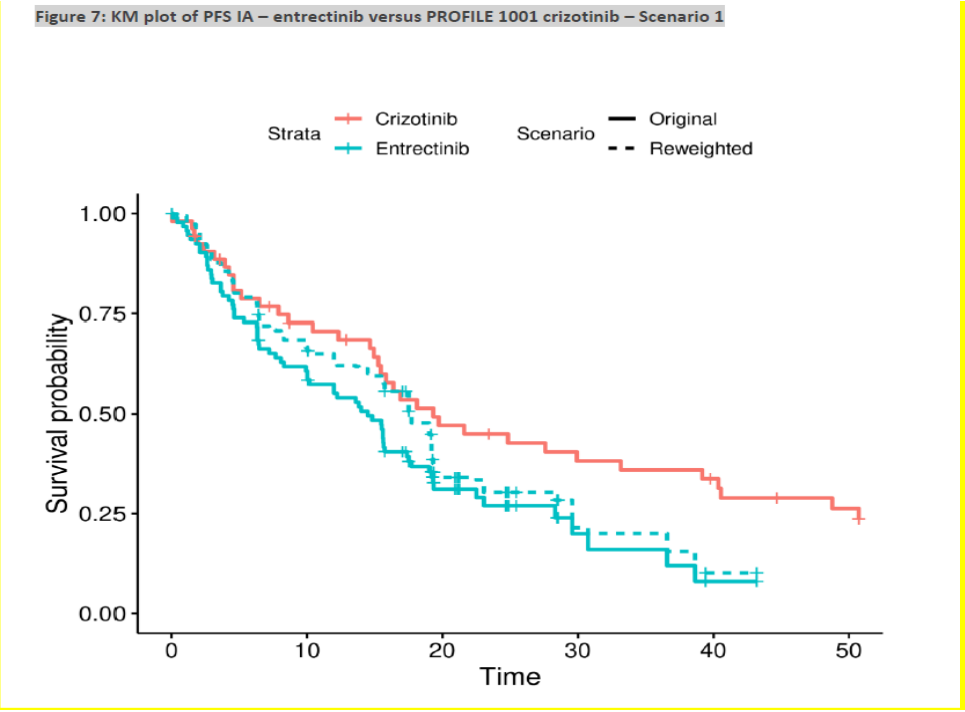
Source: pCODR Submission[35]

Figure 7: Kaplan Meier Plot for Overall Survival: Scenario 3



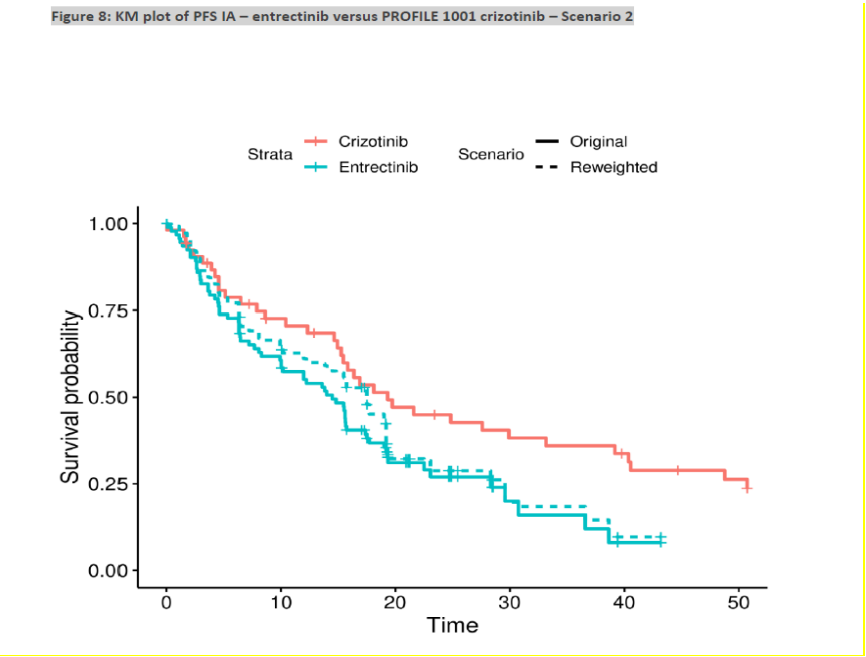
Source: pCODR Submission[35]

Figure 8: Kaplan Meier Plot for Progression Free Survival (Investigator Assessment): Scenario 1



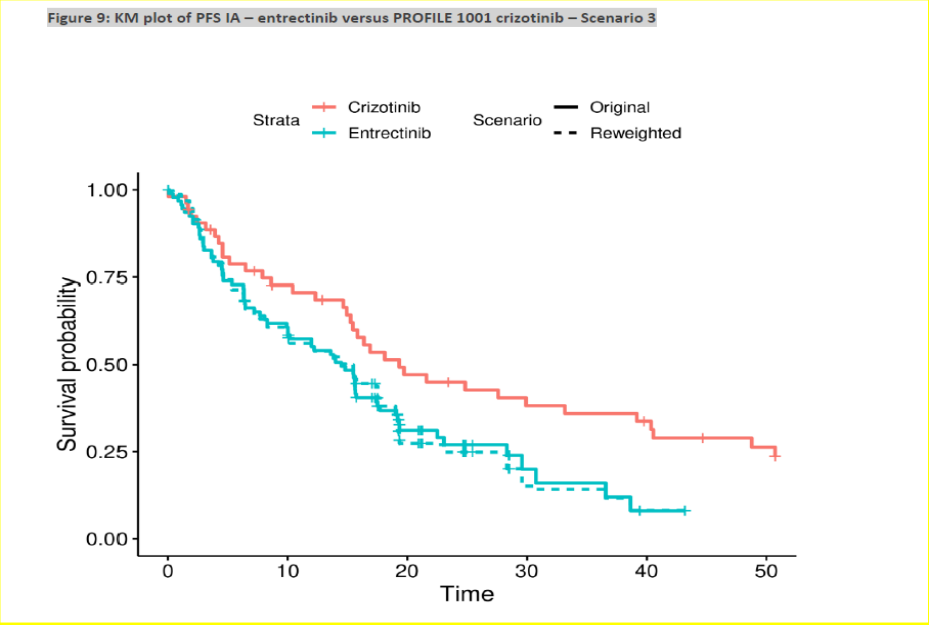
Source: pCODR Submission[35]

Figure 9: Kaplan Meier Plot for Progression Free Survival (Investigator Assessment): Scenario 2



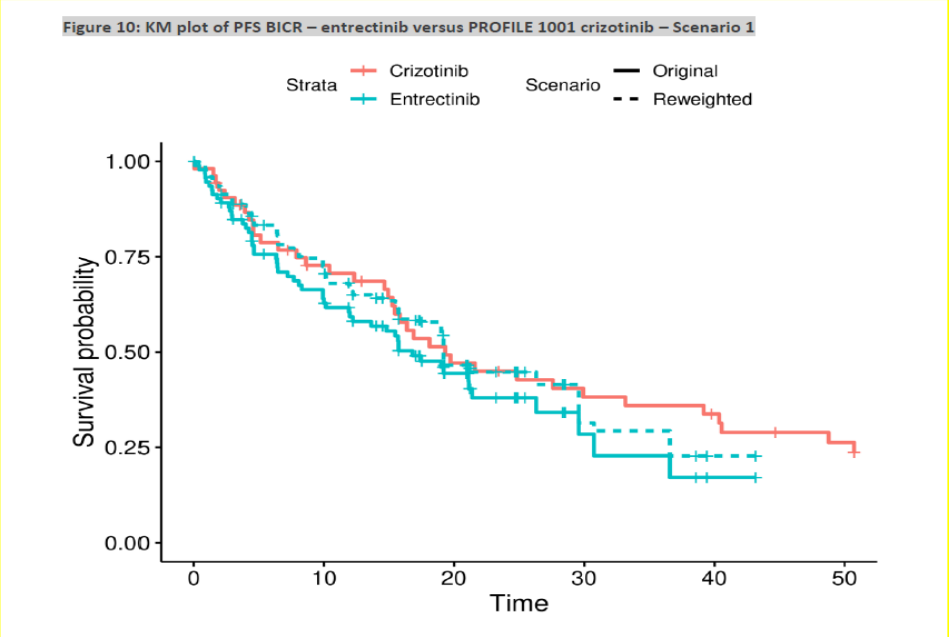
Source: pCODR Submission[35]

Figure 10: Kaplan Meier Plot for Progression Free Survival (Investigator Assessment): Scenario 3



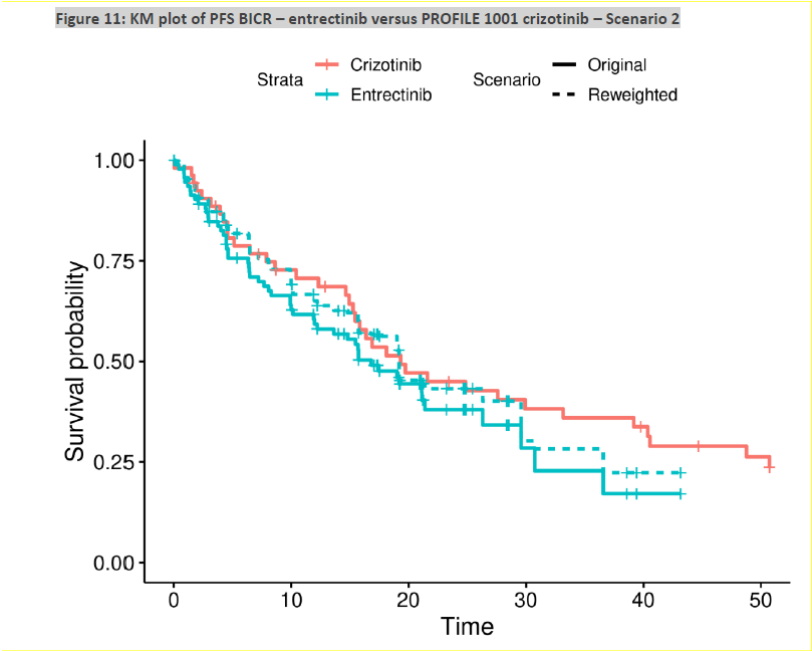
Source: pCODR Submission[35]

Figure 10: Kaplan Meier Plot for Progression Free Survival (BICR): Scenario 1



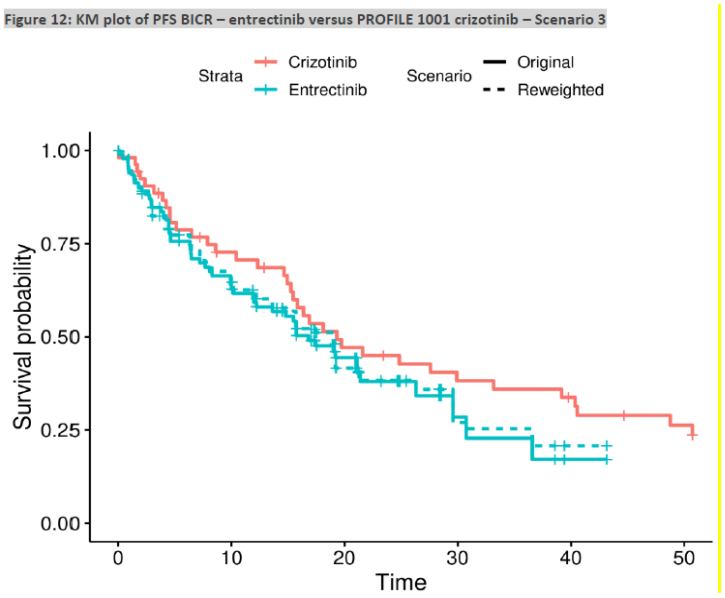
Source: pCODR Submission[35]

Figure 11: Kaplan Meier Plot for Progression Free Survival (BICR): Scenario 2



Source: pCODR Submission[35]

Figure 12: Kaplan Meier Plot for Progression Free Survival (BICR): Scenario 3



Source: pCODR Submission[35]

In addition, a MAIC using the entrectinib integrated analysis and pooled PROFILE 1001 (2019) & Wu (2018) crizotinib data was conducted. Eight variables were attempted for matching in the MAICs (age, sex, smoking status, ECOG PS, disease stage, prior anti-cancer therapy, CNS metastases, and histology). Of these, the sponsor was able to match on the following seven variables: prior treatment, smoking status, age, sex, ECOG PS, CNS metastasis, and histology. The effective sample size for the pooled entrectinib studies was reduced by 39% from 94 patients to 57 patients in the PFS analysis. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment as demonstrated in Table 45.

Table 45: Baseline Characteristics Included in Estimation of MAIC Weights for Entrectinib Versus Crizotinib – Based on PROFILE 1001 + Wu 2018

Arm	Effective sample size	Age, years	% Never smoked	% ECOG 2	% Adeno-carcinoma	% Treatment naïve	% Female	% Stage IV CNS
Pooled Profile 1001 (2019) & Wu (2018) Crizotinib	180	52.5	72.8	0.6	97.2	17.2	57.2	18.1
Entrectinib	94	53.5	59.6	11.7	95.7	33.0	63.8	42.6
Entrectinib re-weighted	(57.3)	52.5	72.8	0.6	97.2	17.2	57.2	18.1

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.

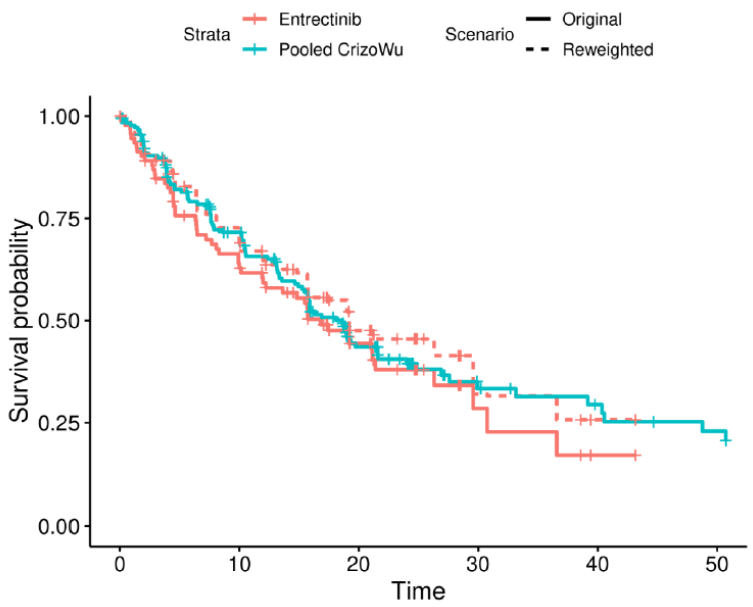
Note: Age is mean for entrectinib, median for crizotinib.

Source: pCODR Submission[35]

For PFS in the MAIC, the estimated the 95% CI did not favour either entrectinib or crizotinib (HR = 0.93; 95% CI: 0.63 to 1.28). The Kaplan Meier curve for PFS is presented in Figure 14 for the MAIC.

Figure 14: Kaplan Meier Plot for Progression Free Survival (BICR)

Figure 1. Kaplan Meier Plot of progression-free survival (PFS BICR) – entrectinib versus pooled Profile 1001 (2019) & Wu (2018) crizotinib



Source: pCODR Submission[35]

MAIC for entrectinib versus docetaxel monotherapy or pemetrexed monotherapy

Eight variables were attempted for matching in the MAICs (age, sex, smoking status, ECOG PS, disease stage, prior anti-cancer therapy, CNS metastases, and histology). Of these, the sponsor was able to match on the following seven variables: disease stage, smoking status, age, sex, ECOG, CNS metastases, and histology. For the PROFILE 1007 trial, the effective sample size for the pooled entrectinib studies was reduced by 52% from 94 patients to 45 in the efficacy analysis and by 34% from 209 to 138 for the safety analysis. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment as demonstrated in Table 46.

Table 46: Baseline Characteristics Included in Estimation of MAIC Weights for Entrectinib Versus Docetaxel Monotherapy or Pemetrexed Monotherapy – Based on PROFILE 1007

Arm	Effective sample size	Age, years	% Never smoked	% ECOG 2	% Adeno-carcinoma	Stage IIIB, %	% Female	% Stage IV CNS
Efficacy								
Chemotherapy	174	49.0	63.8	8.0	94.3	9.2	55.2	34.5
Entrectinib	94	53.5	59.6	11.7	95.7	1.1	63.8	42.6
Entrectinib reweighted	(44.5)	49.0	63.8	8.0	94.3	9.2	55.2	34.5
Safety								
Chemotherapy		49.0	63.8	8.0	94.3	9.2	55.2	34.5
Entrectinib	209	54.9	62.2	8.6	97.1	2.9	61.7	41.1
Entrectinib reweighted	(138.3)	49.0	63.8	8.0	94.3	9.2	55.2	34.5

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.

Note: Age is mean for entrectinib median for chemotherapy.

Source: pCODR Submission[35]

The results for the MAIC comparison of entrectinib versus chemotherapy using data from PROFILE 1007 are presented in Table 47. For OS, the estimated HR favoured entrectinib compared to chemotherapy (0.51, 95% CI: 0.28, 0.77). The Kaplan Meier curve for OS is presented in Figure 15. For PFS, the estimated HR favoured entrectinib compared to chemotherapy (0.26, 95% CI: 0.20, 0.43). The Kaplan Meier curve for PFS is presented in Figure 16. For ORR, the estimated OR favoured entrectinib over chemotherapy (8.1, 95% CI: 5.3, 19.9). For discontinuation due to AEs, neither entrectinib nor chemotherapy was not favoured (OR 0.7; 95% CI: 0.3 to 1.2).

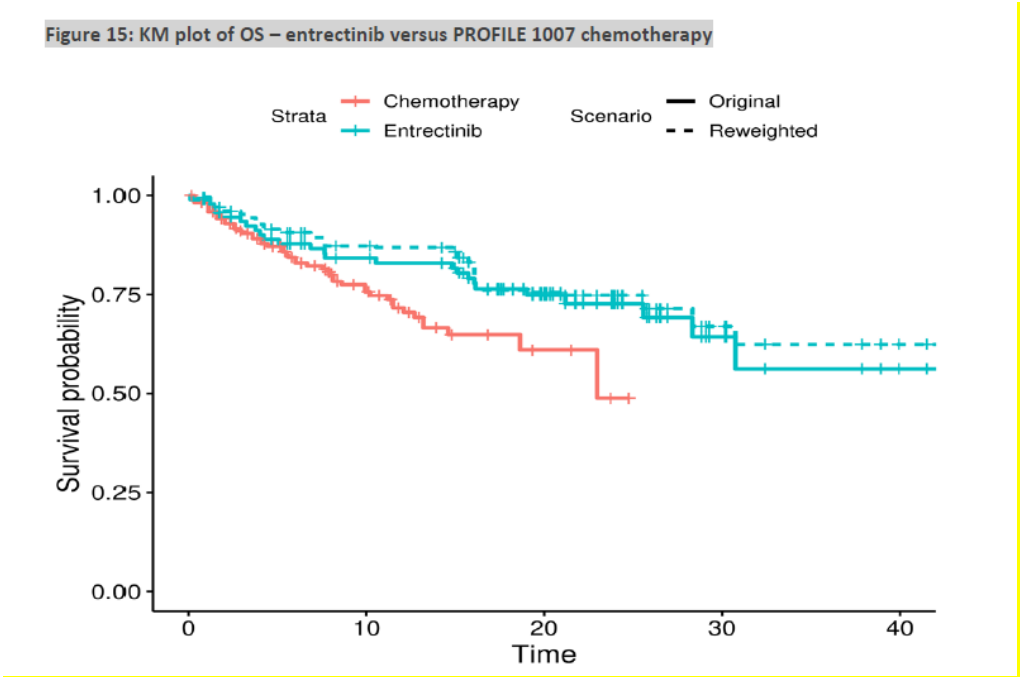
Table 47: MAIC Results for Entrectinib Against Chemotherapy - Based on PROFILE 1007

Outcome	Result
OS, HR (95% CI)	0.51 (0.28, 0.77)[35]
PFS-BICR, HR (95% CI)	0.26 (0.20, 0.43)[35]
ORR, OR (95% CI)	8.1 (5.3, 19.9)[35]
Treatment discontinuation due to AE, OR (95% CI)	0.7 (0.3, 1.2)[35]

AE = adverse events; BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ORR = objective response rate, OS = overall survival.

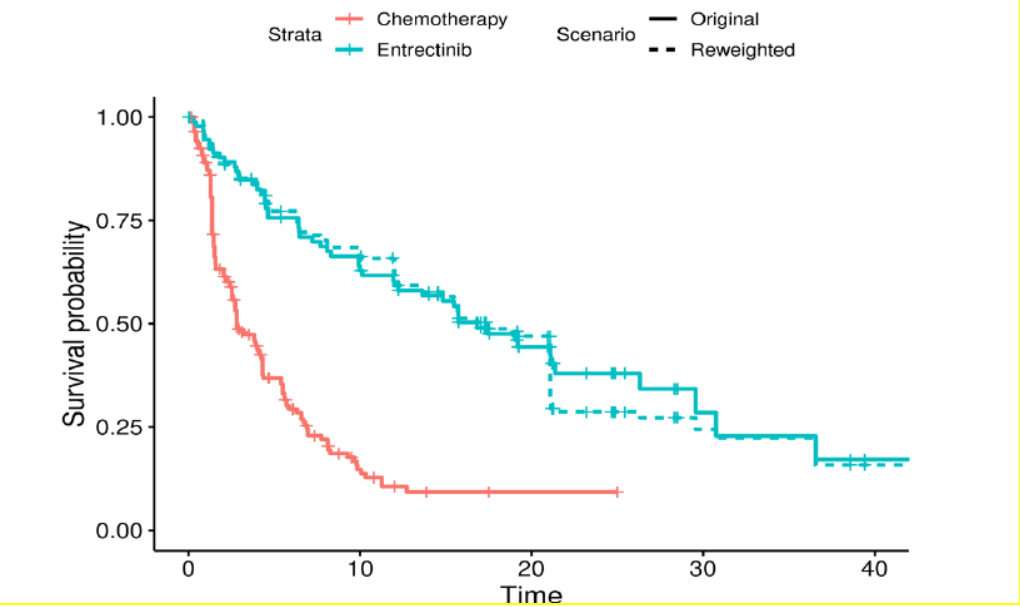
Source: pCODR Submission[35]

Figure 13: Kaplan Meier Plot for Overall Survival



Source: pCODR Submission[35]

Figure 14: Kaplan Meier Plot for Progression Free Survival (BICR)



Source: pCODR Submission[35]

MAIC for entrectinib versus pemetrexed plus platinum and pemetrexed maintenance

Eight variables were attempted for matching in the MAICs (age, sex, smoking status, ECOG PS, disease stage, prior anti-cancer therapy, CNS metastases, and histology). Of these, the sponsor was able to match on the following seven variables: disease stage, smoking status, age, sex, ECOG, CNS metastasis, and histology. For the ASCEND-4 trial, the effective sample size for the pooled entrectinib studies was reduced by 12% from 94 patients to 83 in the efficacy analysis and by 5% from 209 to 199 for the safety analysis. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment as demonstrated in Table 48.

Table 48: Baseline Characteristics Included in Estimation of MAIC Weights for Entrectinib Versus Pemetrexed Plus Platinum and Pemetrexed Maintenance – Based on ASCEND-4

Arm	Effective sample size	Age, years	% Never smoked	% ECOG 2	% Adeno-carcinoma	Stage IIIB, %	% Female	% Stage IV CNS
Efficacy								
Pemetrexed + Platinum + Pemetrexed Maintenance	187	54.0	65.2	5.9	97.9	2.7	61.0	33.2
Entrectinib	94	53.5	59.6	11.7	95.7	1.1	63.8	42.6
Entrectinib reweighted	(83.2)	54.0	65.2	5.9	97.9	2.7	61.0	33.2
Safety								
Pemetrexed + Platinum + Pemetrexed Maintenance		54.0	65.2	5.9	97.9	2.7	61.0	33.2
Entrectinib	209	54.9	62.2	8.6	97.1	2.9	61.7	41.1
Entrectinib reweighted	(199.2)	54.0	65.2	5.9	97.9	2.7	61.0	33.2

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.

Note: Age is mean for Entrectinib, median for ASCEND-4.

Source: pCODR Submission[35]

The results for the MAIC comparison of entrectinib versus pemetrexed plus platinum/pemetrexed maintenance using data from ASCEND-4 are presented in Table 49. For OS, the estimated HR favoured entrectinib over pemetrexed plus platinum/pemetrexed maintenance (0.58, 95% CI: 0.37, 0.87). The Kaplan Meier curve for OS is presented in Figure 17. For PFS, the estimated HR favoured entrectinib over pemetrexed plus platinum/pemetrexed maintenance (0.46, 95% CI: 0.34, 0.6). The Kaplan Meier curve for PFS is presented in Figure 18. The OR for ORR favoured entrectinib over pemetrexed plus platinum/pemetrexed maintenance (8.0, 95% CI: 5.3, 14.4). For discontinuation due to AEs, the OR did not favour entrectinib nor pemetrexed plus platinum/pemetrexed maintenance (0.8, 95% CI: 0.4, 1.2).

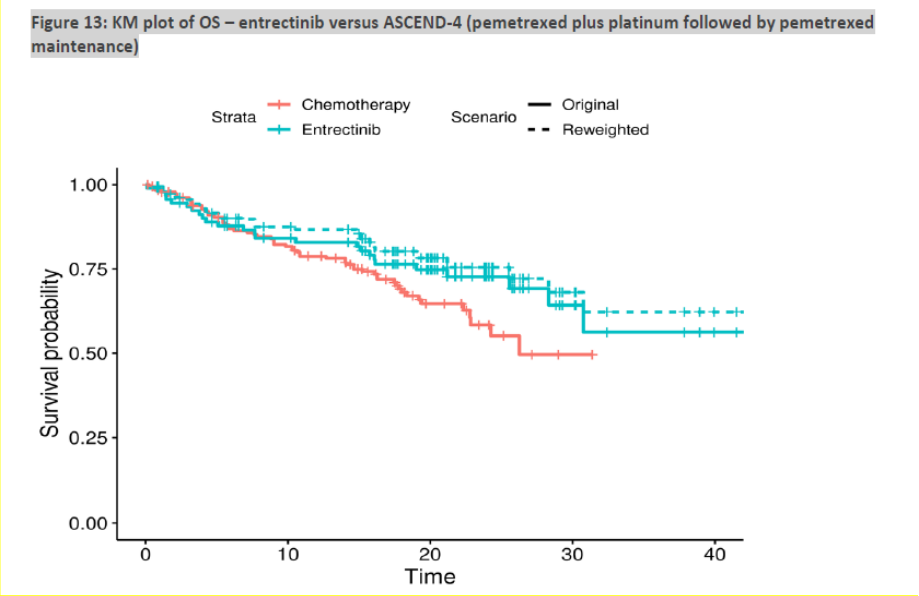
Table 49: MAIC Results for Entrectinib Against Pemetrexed/Platinum - Based on ASCEND-4

Outcome	Result
OS, HR (95% CI)	0.58 (0.37, 0.87)[35]
PFS-BICR, HR (95% CI)	0.46 (0.34, 0.6)[35]
ORR, OR (95% CI)	8.0 (5.3,14.4)[35]
Treatment discontinuation due to AE, OR (95% CI)	0.8 (0.4,1.2)[35]

AE = adverse events; BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ORR = objective response rate; OS = overall survival.

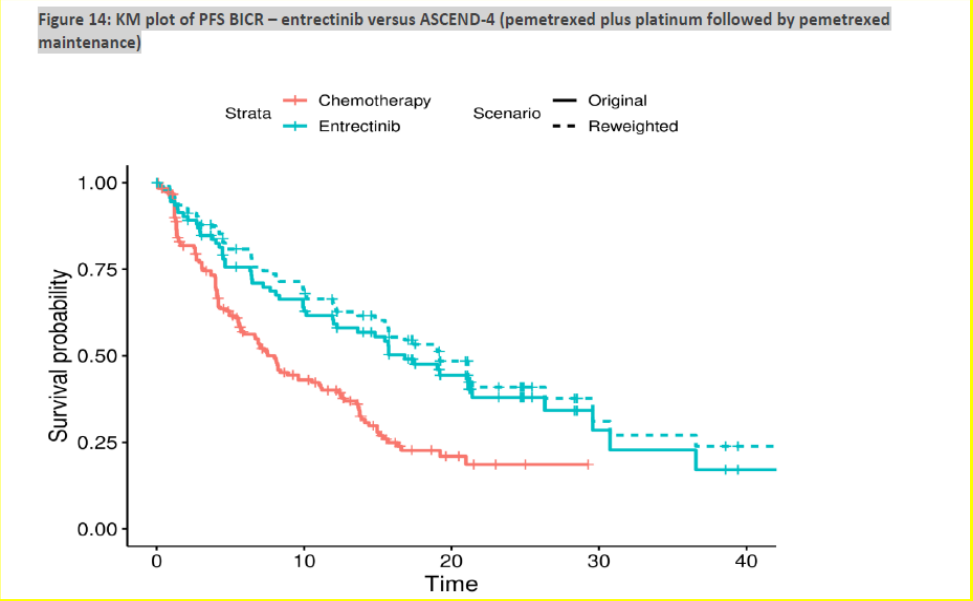
Source: pCODR Submission[35]

Figure 15: Kaplan Meier Plot for Overall Survival



Source: pCODR Submission[35]

Figure 16: Kaplan Meier Plot for Progression Free Survival (BICR)



Source: pCODR Submission[35]

Critical Appraisal

The quality of the sponsor-submitted MAIC was appraised according to best practice principles outlined by Phillippo et al. (2018).[45] The CADTH Methods Team noted the following:

- *Systematic review conduct:* The literature search results may not have captured all relevant trials and the sponsor selected specific studies for inclusion in the MAIC without reporting a rationale for all selections. This may have led to relevant data being excluded in the MAICs.
- *Heterogeneity:* The differences in inclusion/exclusion criteria across the studies introduced heterogeneity, as the index trial with IPD (entrectinib integrated analysis) had broad inclusion criteria, which included patients who received or did not receive prior treatment. Whereas, ASCEND-4 and PROFILE 1007 included only patients who were treatment-naïve or received only one previous treatment. Given that there was no prior matching procedure before weighting to select patients who match on number of prior treatments from the IPD, this heterogeneity was not accounted for in the MAIC. Furthermore, the index trial with IPD included patients with ROS-1 NSCLC; whereas PROFILE 1007 and ASCEND-4 included patients with ALK, which is a different patient population. The proportion of patients with CNS metastasis at baseline was unclearly reported in the PROFILE 1001 trial and as such, three estimates were used that were based on the literature. However, this approach to impute missing values is not an accepted practice; therefore, the results of this MAIC should be regarded with caution. For the PFS estimates, it is unclear how the data were pooled from PROFILE 1001 and Wu 2018. For this, it is recommended that the aggregate studies should first be pooled via meta-analysis and then compared using MAIC but it is unclear whether this was done. For ASCEND-4, the patient population was different (included ALK patients) from the ROS-1 patients included in the pooled entrectinib analysis. All effect modifiers and prognostic variables must be adjusted for in order for a MAIC to be valid, and as such, it is unlikely that this assumption was met. Cross-over to ceritinib was allowed in ASCEND-4 and occurred in 43% of patients, which could bias the results. For PROFILE 1007, the patient population was different (included ALK patients) than the ROS-1 patients included in the pooled entrectinib analysis. Cross-over to crizotinib was allowed in PROFILE 1007 and occurred in 64% of patients, which could bias the results. Furthermore, the entrectinib analysis included a higher proportion of ECOG 2 patients than any other study, which may reflect a patient population with more advanced disease compared with other trials. However, this was adjusted for in the MAIC. Differences existed in the study designs (some were RCTs and some were single arm trials), and this can not be adjusted for in a MAIC. Differences in outcome definitions and assessments (e.g. investigator versus independent review) were not included in matching, which may introduce heterogeneity. Although the inclusion and exclusion criteria for each trial were briefly mentioned, they were not provided in full, which may result in additional differences between the trials. Risk of bias results highlighted major methodological shortcomings across the trials such as a lack of randomization and lack of blinding, which is

more of an issue for harms-related outcomes. Differing lengths of follow-up (ranging from 12.1 to 20.9 months) between the trials can also contribute to heterogeneity, especially for survival analysis, and this was not adjusted for in the MAIC.

- *Selection of variables for matching:* Since these were all unanchored MAICs, both effect modifiers and prognostic variables need to be adjusted for in the analysis. It is unlikely that all effect modifiers and prognostic variables were adjusted for. The MAIC also did not adjust for unknown cross-trial differences; thus, the MAIC estimates are susceptible to bias from unknown confounding. Several variables (e.g., differences in study designs, differences in outcome assessment, and differences in duration of follow-up) were not adjusted for in the MAICs making interpretation of results difficult. Furthermore, it is a requirement in MAICs to assess the degree of residual bias in MAIC estimates. This was not provided in the sponsor's report. Accordingly, the magnitude of the bias in the estimates of the treatment effects remains unknown.
- *Effective sample size:* A comparison of baseline characteristics between the trials pre- and post-matching was provided, which indicated successful matching was obtained for the analysis. For PROFILE 1007, the effective sample size for the entrectinib pooled analysis was reduced by 52% for the efficacy outcomes, which may suggest that these studies should not be analyzed using a MAIC as their patient populations are too heterogeneous. For PROFILE 1001, the effective sample size was reduced by 43% and for ASCEND-4 it was reduced by 12%, which is considered reasonable for a MAIC. Naïve ITCs were not provided as the sponsor noted that this type of analysis is biased and as such, these results could not be compared with the MAIC.
- *Analysis:* Some of the methods used for the MAIC were not appropriate for an unanchored analysis such as selection of one arm in a multi-arm trial for inclusion; not adjusting for all effect modifiers for a variable (CNS metastases) that was not reported in a study based on estimates in the literature; and not analyzing the residual bias for MAIC estimates. To test the proportional hazards assumption, log-log plots and Schoenfeld tests were conducted. Based on the p-values of the diagnostic tests, the assumption of proportionality was likely upheld.[28] For the time to event analyses, extrapolation of long-term survival from short term follow-up carries high uncertainty and risk of bias. Results on important variables such as health-related quality of life, were not included in the MAIC. Based on all of these limitations, no comparisons can be made across these MAICs as they are based on different weightings and have adjusted for different factors.
- *PFS estimates for crizotinib:* PFS estimates were provided for the PROFILE 1001 study in a MAIC for crizotinib versus entrectinib from the integrated analysis. A subsequent analysis was conducted where PROFILE 1001 was pooled with the Wu 2018 study. This led to results that favoured entrectinib; although, they were not statistically significant.

7.1.3 Summary

The sponsor conducted ITC analyses to provide comparative efficacy estimates between entrectinib and relevant comparators for first-line treatment of adult patients with ROS-1 NSCLC. The ITCs performed included MAIC analyses to derive comparative estimates for the outcomes of OS, PFS, ORR, and discontinuation due to AEs. The methods and results of the ITCs were critically appraised by the CADTH Methods Team according to best practice principles for MAICs.[45] For entrectinib versus crizotinib, the results were not statistically significant across all outcomes (based on PROFILE 1001 and the pooled PFS results for PROFILE 1001 and Wu 2018). For entrectinib versus chemotherapy, the results were statistically significantly in favour of entrectinib for OS, PFS, and ORR (based on PROFILE 1007). No statistically significant differences were observed for discontinuation due to AEs. For entrectinib versus pemetrexed/platinum, the results were statistically significantly in favour of entrectinib for OS, PFS, and ORR (based on ASCEND-4). No statistically significant differences were observed for discontinuation due to AEs. The CADTH Methods Team concluded the ITC results should be interpreted with extreme caution considering several limitations associated with the analyses, such as substantial heterogeneity between studies, inability to adjust for all potential confounders and prognostic variables, and use of inappropriate analysis methods for MAIC. Overall, due to the limitations identified, the findings from the MAIC were inconclusive because the assumptions used for the unanchored analyses are impossible to meet and present an unknown amount of bias in the unanchored estimate.

7.2 Critical Appraisal of the Sponsor-Submitted Propensity Score Analysis Using Real-World Data

7.2.1 Objective

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the PE model submitted for this submission. Consequently, the sponsor supplied a propensity score analysis using real-world data from the Flatiron Health Analytic Database.[46] The objective of the propensity score analysis was for the comparative analysis between crizotinib and entrectinib among ROS-1 NSCLC patients for time to treatment discontinuation (primary outcome), OS, and PFS (secondary outcomes). Results of the propensity score analysis were subsequently incorporated into the PE model to help inform cost-effectiveness estimates for entrectinib.

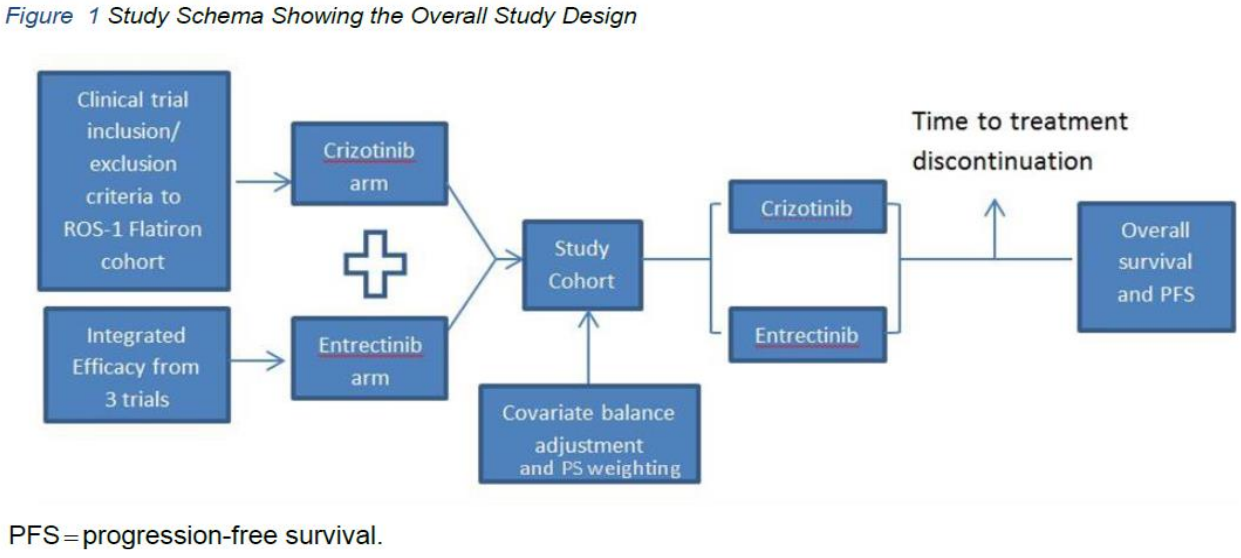
7.2.2 Findings

The sponsor submitted a propensity score analysis as part of the submission, which has been described and critically appraised in the sections below.

Methods

The sponsor conducted a propensity score analysis using the integrated entrectinib analysis for the three open-label, single-arm trials (ALKA, STARTRK-1, STARTRK-2) referred to as the entrectinib arm compared with patients who received crizotinib from the Flatiron Health Analytic Database from electronic medical records of oncology centres in the United States referred to as the crizotinib arm. The overall study design is presented in Figure 19.[46]

Figure 17: Overall study design for Propensity Score Analysis for Entrectinib versus Crizotinib (based on the Flatiron study)



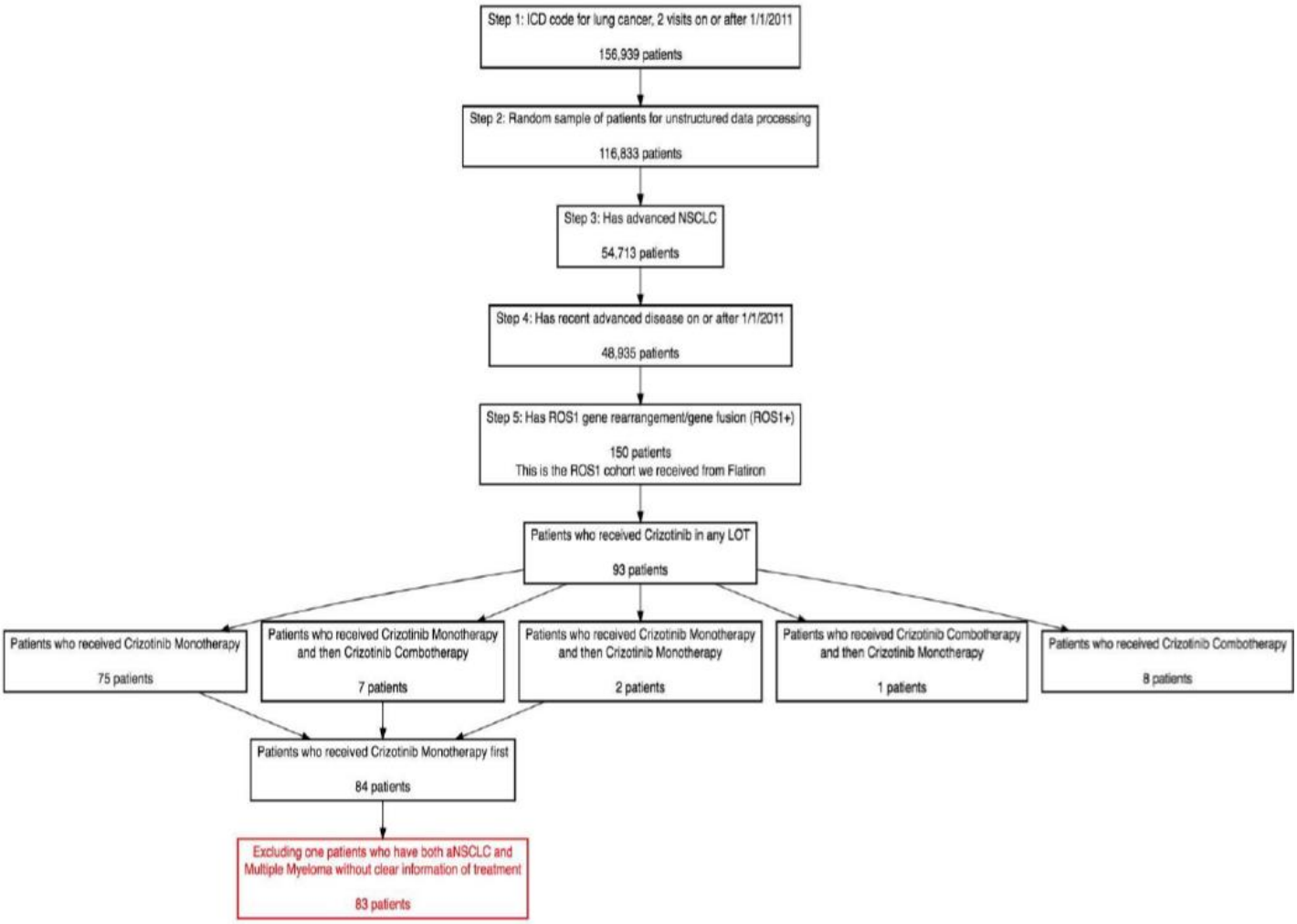
Source: Submission materials[46]

Study population

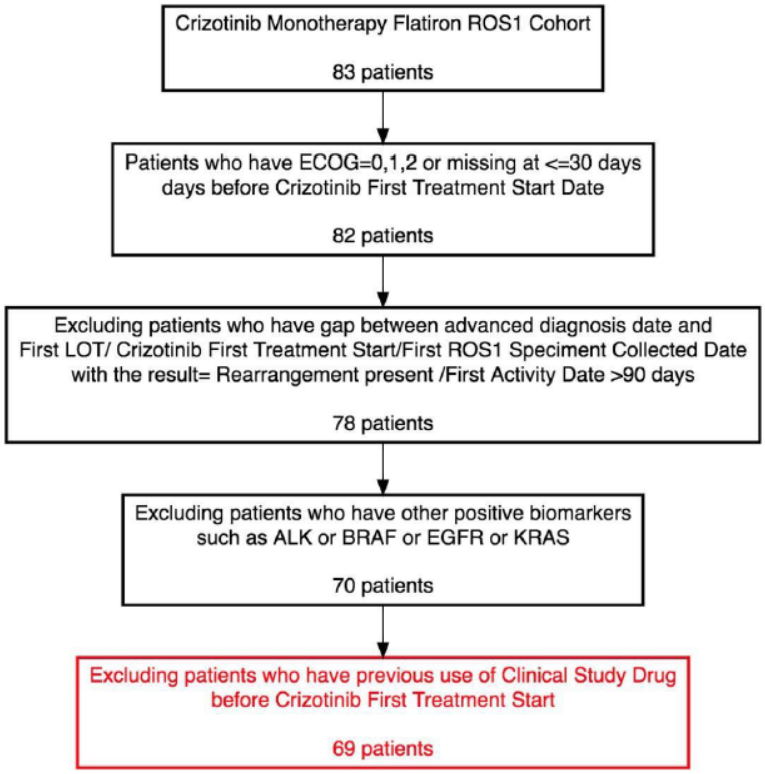
Entrectinib arm: For the entrectinib arm, patients were included if they had advanced or metastatic NSCLC between December 2013 and November 2017 who were adults aged 18 years and older with ECOG PS 0-2 and treated with entrectinib. The index date was the date of initiation of treatment with entrectinib and patients were followed up until either date of discontinuation of treatment or death, with patients being censored if they were still on treatment at end of follow-up or lost to follow-up at the last activity date or visit. ROS-1 status was confirmed using NGS or other nucleic acid diagnostic tests. Prior anticancer treatment was allowed with chemotherapy but not with a ROS-1 inhibitor (e.g. crizotinib). Patients who had a history of cancer other than in the lung were eligible for inclusion but patients with concurrent malignancies in the lung and other areas were excluded. A total of 94 patients from Italy, South Korea, United States, Australia, United Kingdom, Netherlands, Singapore, Spain, Taiwan, Belgium, France, Germany, Hong Kong, Japan, and Poland were included in the entrectinib arm.

Crizotinib arm: For the crizotinib arm, patients were included if they had advanced or metastatic NSCLC diagnosed between January 2011 and June 2018 who were adults aged 18 years and older with ECOG PS 0-2 (missing ECOG were allowed) and treated with crizotinib as monotherapy for the first time. The index date was the date of initiation of treatment with crizotinib and patients were followed up until either date of discontinuation of treatment or death or last activity, with patients being censored if they were still on treatment at end of follow-up or lost to follow-up at the last activity date or visit. ROS status was confirmed using NGS, FISH, or IHC. Prior anticancer was allowed but not with a ROS-1 inhibitor. Patients with a gap of more than 90 days between their diagnosis date and start date with crizotinib were excluded if no information was available on prior treatment. Additional criteria were applied to the crizotinib arm to make the analysis more consistent with the entrectinib arm. The following patients were excluded: one patient with an ECOG PS >2 (but patients with missing ECOG were allowed), four patients with a gap (of > 90 days) between their diagnosis and treatment initiation, eight patients with concomitant oncodriver mutations, and one patient due to the use of a previous clinical study drug prior to initiating treatment with crizotinib. Based on these criteria, 69 patients were included in the crizotinib (Flatiron) arm and all were from the United States. The flow of these patients can be found in Figure 20.[46]

Figure 18: Flow of Patients in the Crizotinib Arm (based on the Flatiron study)



ECOG = Eastern Cooperative Oncology Group, LOT = list of therapy, NSCLC = non-small cell lung cancer.



Source: Submission materials[46]

Matching and Statistical Analysis

The primary endpoint was time to treatment discontinuation. In the entrectinib arm, this was defined as the date from initiation of entrectinib to treatment discontinuation; disease progression was confirmed by BICR RECIST v1.1 criteria. Treatment beyond progression was at the discretion of the investigator and efficacy was based on the first documented radiographic progression according to RECIST v1.1 via BICR regardless of whether treatment beyond progression occurred or not. Demographic data and tumour-related information was obtained at treatment initiation. PFS was defined as the number of months from administration of entrectinib to disease progression according to BICR RECIST v1.1 or death due to any cause, whichever occurred first. OS was defined as time from entrectinib initiation to death of any cause.

In the crizotinib arm, treatment start and stop dates were obtained using technology-enabled data abstraction methods from the patients' medical records. Treatment discontinuation was defined as the patient using another line of therapy, patient dying within seven days of the last administration of treatment, duration was 60 days or more between last drug episode date and last visit date, or disease progression as per physician documentation. Treatment beyond progression was routinely observed for patients on crizotinib who were perceived to still derive clinical benefit. Since differences in the treatment beyond progression definitions may introduce bias, in the crizotinib arm, the date from initiation of treatment to evidence of real-world progression was used when treatment beyond progression was observed. When real-world progression occurred less than 10 days after starting crizotinib, the second progression event was considered evidence of real-world progression because the first progression could be attributable to previous treatment and not crizotinib. Demographic data and tumour-related information was obtained at treatment initiation or if this information was not available at this timepoint, the closest possible previous visit or encounter was used. PFS was assessed through tumour growth by scans, pathology, and/or clinician determination according to the clinician's notes in the electronic medical record, loss of clinical benefit, or both using the date of treatment progression described earlier in this section. OS was defined as date from crizotinib initiation to death of any cause.

Data analysis for demographics included chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Six steps were used to calculate PFS and OS as follows 1) description of baseline characteristics (including prior lines of treatment), 2) selection of prognostic variables through literature review and expert opinion, 3) construction of propensity scores using prognostic factors from Step 2 through the inverse probability of treatment weighting truncated at the 99th percentile for variables that were included in the dataset only. The propensity score distribution was assessed using graphical display and the balance of prognostic factors was assessed using weighted standardized means, 4) time to event analysis was conducted using Kaplan Meier curves and weighted log-rank tests, 5) weighed Cox proportional hazard models used to estimate the treatment effect of entrectinib vs crizotinib with 95% confidence intervals, and 6) sensitivity analysis was performed.

Unconditional logistic regression was used to estimate propensity scores by incorporating predictors of treatment assignment. The following variables were considered for matching: age, gender, race, history of smoking, previous type of treatment, and CNS metastases at baseline. To obtain a weight for each patient included in the comparative analysis, inverse probability of treatment weighting was used for propensity scores using the average treatment effect on the treated (ATT) approach with the entrectinib arm as the reference population. To control for extreme weights, they were truncated at the 95th percentile. For this, the number of weighted patients is calculated by the sum of each weight we assigned by propensity score for a patient to the weighted population.[28] For example, patient A can have a weight of 0.6 (i.e. contributing as 0.6 patient in the weighted population) and patient B can have a weight of 0.3 (meaning contribution as 0.3 patient in the weighted population). This all depends on their patient characteristics. Accordingly, some patients contributed weights > 1 to the weighted population (for example, patient A now can be counted as three patients in the weighted population).

Differences in PFS and OS were examined using the log-rank test and treatment effects between the two arms were examined using multi-variable Cox proportional hazard model adjusted by covariates used in development of the propensity score to remove potential additional residual confounding from adjusted covariates. To test the validity of proportional hazard assumptions, plots of the negative log of the survival function and Schoenfeld residual plots were used. Sensitivity analyses were conducted including restricting the analysis to those patients with 12 months or more follow-up and restricting to those patients with ECOG PS data in Flatiron (i.e. only patients with no missing ECOG PS reports).

Results

Baseline demographics between the two arms are presented in Table 49 prior to propensity score matching. The median duration of follow-up was 13.09 months in the crizotinib arm (Q1-Q3: 4.08, 17.63 months) and 19.34 months in the entrectinib arm (Q1-Q3: 7.66, 24.34 months). On average, before propensity score matching, patients in the entrectinib arm were younger and there was a higher percentage of patients who were Asian, male, and had a history smoking. As well, a higher percentage of patients in the entrectinib arm had CNS metastasis at treatment initiation, a higher volume of tumour burden, and were more heavily pretreated than the crizotinib arm. Importantly, 55% of patients in the crizotinib arm were missing ECOG PS values. Location of where data was obtained differed as 100% of the locations in the crizotinib arm were in the US; whereas, 45.7% of the trial sites were in the Asia Pacific, 27.7% in Europe, and 26.6% in the US for the entrectinib arm.

Figure 19: Baseline Demographic and Clinical Characteristics of the Entrectinib and Crizotinib Arms

Category	Sub□category	Trial Entrectinib (N=53)	Trial Entrectinib (N=94)	RWD Crizotinib (N=69)
Gender n (%)	Female	34 (64.15)	60 (63.83)	39 (56.52)
	Male	19 (35.85)	34 (36.17)	30 (49.48)
Race n (%)	Asian	19 (35.85)	41 (43.62)	6 (8.7)
	White	31 (58.49)	46 (48.94)	41 (59.42)
	Black or African American	2 (3.77)	4 (4.26)	8 (11.59)
	Hispanic or Latino	1 (1.89)	1 (1.06)	10 (14.49)
	Not Provided	0 (0.0)	2 (2.13)	4 (5.8)
Age (%)	18-34 years old	3 (5.66)	7 (7.45)	0 (0)
	35-64 years old	39 (73.58)	67 (71.28)	32 (46.38)
	ε65 years old	11 (20.75)	20 (21.28)	37 (53.62)
Age Median (IQR) (Age=Year of First Treatment Start=Birth Year)		53 (46□61)	53 (45-62)	65 (55□73)
BMI (%)	Underweight<18.5 (kg/m²)	2 (3.7)	5 (5.32)	0 (0)
	Normal 18.5<25 (kg/m²)	25 (47.17)	50 (53.19)	15 (21.74)
	Overweight 25<30 (kg/m²)	14 (26.42)	24 (25.53)	18 (26.09)
	Obese ≥30 (kg/m²)	12 (22.64)	15 (15.96)	14 (20.29)
	Not Provided	0 (0)	0(0)	22 (31.88)
BMI Mean (SD; baseline assessed≤30 days before first treatment)		25.93 (5.05)	25.01 (5.02)	27.77 (5.57)
Smoking Status n (%)	History of smoking	22 (41.51)	38 (40.43)	38 (55.07)
	No history of smoking	31 (58.49)	56 (59.57)	31 (44.93)
Location of clinical practice n (%)	Asia Pacific	19 (35.8)	43 (45.7)	0 (0)
	Europe	19 (35.8)	26 (27.7)	0 (0)
	USA	15 (28.3)	25 (26.6)	69 (100.0)

Source: Submission materials[46]

Figure 20: Baseline Demographic and Clinical Characteristics of the Entrectinib and Crizotinib Arms (cont.)

Category	Sub□category	Trial Entrectinib (N=53)	Trial Entrectinib (N = 94)	RWD Crizotinib (N=69)
ECOG n (%; baseline assessed≤30 days before First Treatment Start Date for RWD)	0	20 (37.74)	35 (37.23)	16 (23.19)
	1	27 (50.94)	48 (51.06)	8 (11.59)
	2	6 (11.32)	11 (11.7)	7 (10.14)
	Missing	0(0)	0(0)	38 (55.07)
Brain Mets at baseline n (%; before or on First Treatment Start)	Yes	23 (43.4)	40 (42.55)	17 (24.64)
	No	30 (56.6)	54 (57.45)	52 (75.36)
Total Number of Mets sites (Note: Other Met is considered as 1) before or on Index Date n (%)	≤2	27 (50.9)	50 (53.0)	50 (72.5)
	>2	26 (49.1)	44 (47.0)	19 (27.5)
Number of prior LOT	<2 LOT	40 (75.47)	70 (74.47)	63 (91.3)
	≥2 LOT	13 (24.53)	24 (25.53)	6 (8.7)
Any prior target therapies n(%)	Yes	9 (16.98)*	13 (13.83)	11 (15.94)
Any prior chemotherapies n(%)	Yes	34 (64.15)	67 (71.28)	21 (30.43)

Source: Submission materials[46]

Treatment beyond progression was observed in 27 out of 41 patients in the crizotinib arm with a subsequent recording of treatment discontinuation, death or switching of treatment.

The baseline characteristics of patients in the crizotinib and entrectinib arms in the propensity score matching process are summarized in Table 51; namely, there were 78 patients in the crizotinib arm and 94 in the entrectinib arm. Weighted standard mean differences (SMD) were calculated between the groups, with values below 0.2 deemed acceptable due to the low sample size and limited number of variables for balancing the arms. Prior to weighting, the SMDs ranged from 0.15 (gender) to 0.91 (age). After weighting, all SMDs were less than 0.2, except for prior therapy, which had a SMD of 0.21. The proportional hazards assumption was tested statistically and it was met for all outcomes.[46]

Figure 21: Propensity Score Matching Diagnosis for the Entrectinib and Crizotinib Arms

	All Population Not Weighted				Matched Population-ATT (Truncated Sample)			
	Crizotinib Arm Number (%)	Entrectinib Arm Number (%)	p Value	SMD	Crizotinib Arm Number (%)	Entrectinib Arm Number (%)	p Value	SMD
n	69	94			78	94		
Gender	30 (43.5)	34 (36.2)	0.434	0.15	33.3 (42.7)	34.0 (36.2)	0.483	0.134
Race	41 (59.4)	46 (48.9)	0.243	0.212	41.6 (53.2)	46.0 (48.9)	0.655	0.086
Age	64.33 (11.77)	53.52 (12.09)	<0.001	0.906	55.62 (10.35)	53.52 (12.09)	0.278	0.186
Brain Metastasis	17 (24.6)	40 (42.6)	0.028	0.386	34.1 (43.6)	40.0 (42.6)	0.914	0.021
Prior Lines Therapy	6 (8.7)	24 (25.5)	0.011	0.459	13.3 (17.0)	24.0 (25.5)	0.328	0.209
History of Smoking	31 (44.9)	56 (59.6)	0.09	0.296	47.2 (60.4)	56.0 (59.6)	0.929	0.017

ATT = weights for average treatment effect on the treated; SMD = standardized mean difference; Grouping in variables as reported previously.

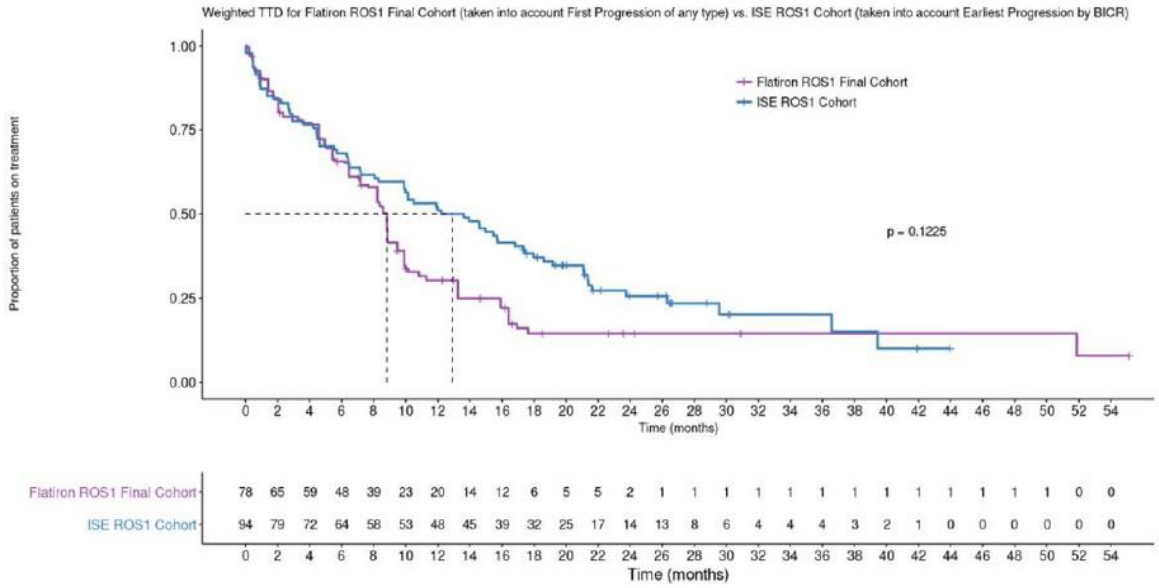
Source: Submission materials46

Time to treatment discontinuation

There were 71 patients in the entrectinib arm and 50 patients in the crizotinib arm who discontinued treatment. The median time to treatment discontinuation in the entrectinib arm including 94 patients was 12.9 months (95% CI: 9.9, 17.4). For the crizotinib arm, the time to treatment discontinuation prior to weighting was 8.4 months (95% CI: 6.2, 10.1), which increased to 8.8 months (95% CI: 7.2, 9.9) after weighting. The unadjusted HR was 0.74 (95% CI: 0.51, 1.08). The propensity score weighted Cox proportional hazard model suggested a lower hazard for treatment discontinuation with entrectinib compared to crizotinib (HR: 0.68; 95% CI: 0.47, 0.98). The Kaplan Meier curves for time to treatment discontinuation are presented in Figure 21.[46]

Figure 22: Time to treatment discontinuation Kaplan Meier Curves

Figure 7 Kaplan Meier Estimates of Weighted TTD across the Arms (BICR)



BICR = blinded independent central review; ISE = integrated summary of efficacy; TTD = time to treatment discontinuation.

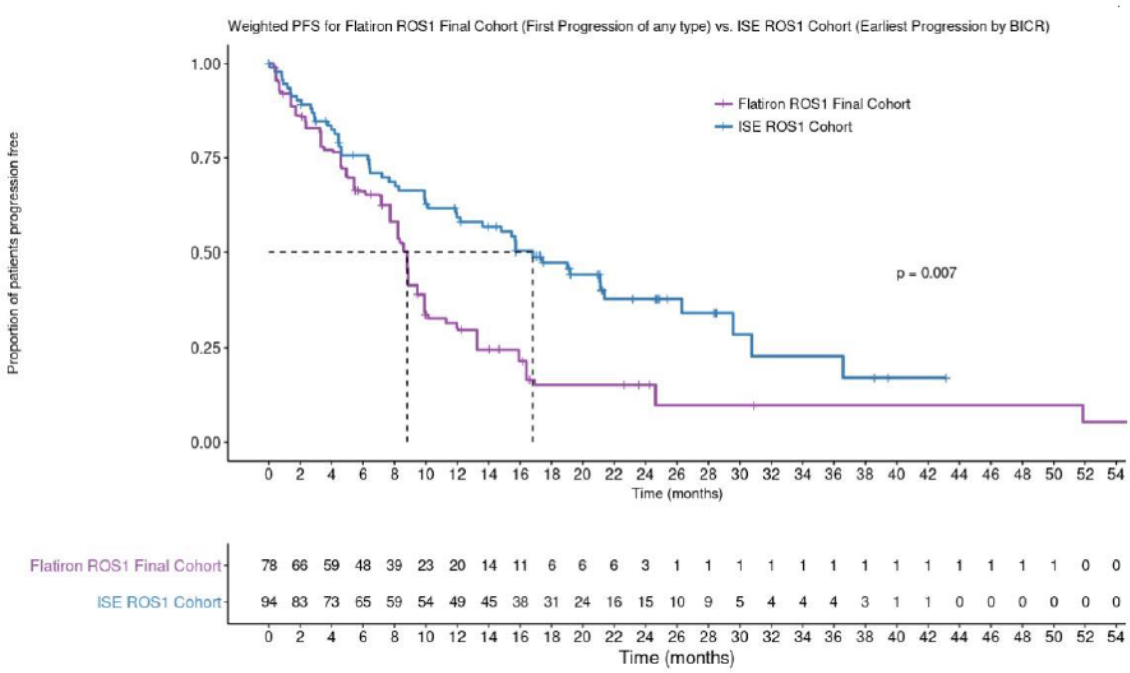
Source: Submission materials[46]

Progression Free Survival

There were 54 patients in the entrectinib arm and 50 patients in the crizotinib arm who had disease progression or death. The median PFS was 16.8 months (95% CI: 12.0, 26.3) for the entrectinib arm. For the crizotinib arm, PFS prior to weighting was 8.5 months (95% CI: 6.2, 10.1), which increased to 8.8 months (95% CI: 7.7, 9.9) after weighting. The unadjusted HR was 0.56 (95% CI: 0.39, 0.84). The propensity score weighted Cox proportional hazard model suggested entrectinib was favoured over crizotinib for PFS (HR 0.51, 95% CI 0.34, 0.75). The Kaplan Meier curves for PFS are presented in Figure 22.[46]

Figure 23: Progression Free Survival Kaplan Meier Curves

igure 8 Kaplan Meier Estimates of Weighted PFS across the Arms (BICR)



BICR = blinded independent central review; ISE = integrated summary of efficacy; PFS = progression-free survival.

Source: Submission materials46

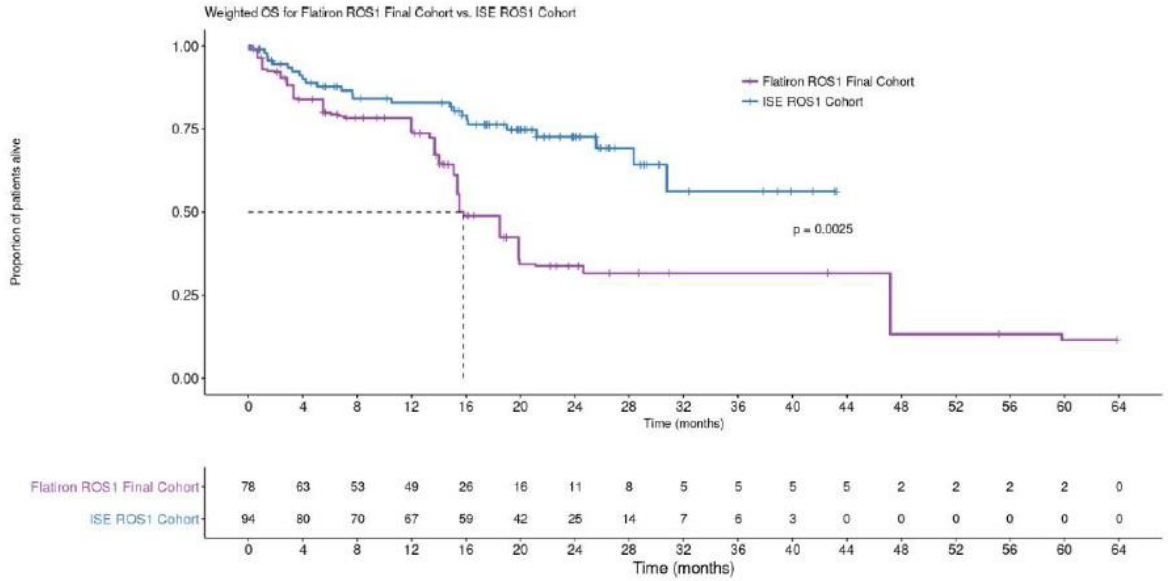
Overall Survival

The unadjusted HR for OS was 0.44 (95% CI: 0.26, 0.75). The propensity score weighted Cox proportional hazard model suggested entrectinib was favoured over crizotinib for OS (HR 0.39, 95% CI: 0.23, 0.65). The Kaplan Meier curves for OS are presented in Figure 23.

Figure 24: Overall Survival Kaplan Meier Curves

Figure 9 Kaplan Meier Estimates of OS (Weighted OS for the Crizotinib Arm)

Figure 9 Kaplan Meier Estimates of OS (Weighted OS for the Crizotinib Arm)



ISE = integrated summary of efficacy; OS = overall survival.

Source: Submission materials46

Critical Appraisal – Limitations and Sources of Bias

The pCODR Methods Team identified a number of limitations of the propensity score matching analysis[47], summarized below, which should be considered when interpreting the results.

- Outcome definition: The time to progression variable was extracted retrospectively from real world data collected in electronic health records. This is conceptually different from collection of documented progression data from clinical trials, which is collected prospectively.[21] The start and end dates of treatment are crucial for the determination of time to treatment discontinuation and it is unclear how many patients in the crizotinib arm had ambiguous start and or end dates[46] PFS was also assessed differently between the treatment arms; namely, independent investigator assessment or BICR as per RECIST was used in the entrectinib arm versus scans at various timepoints were used in the crizotinib arm. The reason for treatment discontinuation was not recorded for the crizotinib arm yet was available for the entrectinib arm.[46] This means that the two arms are not comparable regarding the outcomes examined and the results should be interpreted with caution.
- Baseline patient characteristics: There were a number of patients with missing ECOG values in the crizotinib arm who were included in the analysis, which could have biased the results. For example, if these patients had an ECOG >2, they would be considered a sicker patient population than those in the entrectinib arm, which would bias the results in favour of entrectinib. Furthermore, varying follow-up times were observed in the crizotinib arm. However, this was addressed through the additional sensitivity analyses performed to examine the robustness of the primary analysis, which might mean that these factors did not substantially impact the results.[21] The entrectinib arm comprised of patients who were followed up for ≥12 months after the first response, which was not the case for the crizotinib arm and may compromise the results of comparative analyses due to

heterogeneity between the two arms. Furthermore, one arm came from a real-world data study and the other from a trial; therefore, the propensity score method may not address differences in study designs.[21] For the entrectinib arm, patients had a documented response to treatment. However, the patients included the crizotinib arm were selected based on their electronic health records as treated. This suggests that the arms are not comparable, which could compromise the results.

- Confounding variables: Adjustments for all confounding variables must be performed for propensity scores to be valid; thus, it is unlikely that this criterion was met. Namely, several variables (e.g., disease stage, ECOG PS, histology, differences in study designs, differences in outcome assessment, and differences in duration of follow-up) were not adjusted for in the propensity scores; therefore, matching on all potential confounders was impossible. Accordingly, residual confounding may exist.[46]

7.2.3 Summary

In the absence of RCTs comparing entrectinib to relevant comparators, a propensity score matching comparison analysis was performed to provide an estimate of the treatment effect of entrectinib from the integrated analysis compared to patients treated with crizotinib from a real-world data study. Data on crizotinib came from electronic health records from multiple sources in the United States. Propensity score matching was used to derive comparative estimates for the time to treatment discontinuation, PFS, and OS between patients treated with entrectinib and crizotinib. The patients in the crizotinib study were propensity score matched to patients in the entrectinib integrated analysis on the following gender, race, age, smoking history, brain metastases, and prior line of therapy. The propensity score matching process increased the effective sample size from 69 to 78 patients in the crizotinib arm. The propensity score analysis produced an HR of 0.68 (95% CI: 0.47, 0.98) favouring entrectinib over crizotinib for treatment discontinuation. For PFS, the HR was 0.51 (95% CI: 0.34, 0.75), which also suggests that entrectinib is favoured over crizotinib in the propensity score analysis. The OS favoured entrectinib over crizotinib (HR 0.39, 95% CI: 0.23, 0.65). The CADTH Methods Team concluded that the results from the propensity score matching analyses should be interpreted with extreme caution considering several limitations. The most significant of these limitations included 1) one arm came from a real-world data study and the other from a trial; therefore, the propensity score method may not address differences in study designs and 2) the omission of important variables from the matching process, which may confound the treatment effect estimates obtained. The treatment effect estimates obtained in the propensity score analysis are likely biased and not solely due to the effects of the treatments examined, and therefore, should be interpreted with extreme caution.

In order to compare entrectinib to crizotinib a MAIC (described and assessed in section 7.1) and a propensity score analysis (described and assessed in section 7.2) were performed. For the MAIC the results were not statistically significant different between entrectinib and crizotinib. The results of the propensity score analyses suggested that entrectinib was favored over crizotinib. The CADTH Methods Team considered the credibility (internal validity) of the comparative estimates to crizotinib to be very low. As a result, the estimates may over- or underestimate the true treatment effect associated with entrectinib compared with crizotinib. The CADTH Methods Team highlighted given the uncertainty in both the MAIC and propensity score analysis, the MAIC results were more conservative as it did not show any significant differences between entrectinib and crizotinib. This aligned with the CGP who noted that there is currently insufficient evidence to choose one of the drugs (i.e., entrectinib or crizotinib) over the other.

8 Comparison with Other Literature

The sponsor included treatment estimates for crizotinib versus pemetrexed-plus-platinum chemotherapy from the PROFILE 1014 trial[4] in the PE model to help inform cost-effectiveness estimates for entrectinib. Therefore, the results of the PROFILE 1014 trial are summarized in this section. PROFILE 1014 was a randomized, open-label, phase 3, international trial comparing crizotinib (n = 172 patients) with pemetrexed-plus-platinum chemotherapy (n = 171 patients). Patients were included if they had ALK positive NSCLC and did not receive previous systemic treatment; however, patients with treated brain metastases were included if they were neurologically stable for at least two weeks prior to enrollment and did not require ongoing glucocorticoid treatment. Additional criteria were age 18 years and above, measurable disease as per RECIST version 1.1, ECOG PS 0 to 2, and adequate hepatic/renal/bone marrow function. Patients were randomized to either 250 mg twice daily oral crizotinib or intravenous pemetrexed (500 mg per square metre of body-surface area) plus either cisplatin (75 mg per square metre) or carboplatin (target area under the curve of 5 to 6 mg per milliliter per minute) every three weeks up to a maximum of six cycles. If safety screening criteria were met, patients could cross over to crizotinib if disease progression was confirmed by independent radiologic review. PFS was defined as either death or the time from randomization to RECIST-defined progression by independent radiologic review.

The baseline patient characteristics of the intention-to-treat population were as follows: median age was 52 years in the crizotinib arm versus 54 in the chemotherapy arm; percentage of female patients was 60% in crizotinib versus 63% in chemotherapy; race breakdown reported in the order of White, Asian, and Other was 53%, 45%, and 2%, respectively, in the crizotinib arm versus 50%, 47%, and 4%, respectively, in the chemotherapy arm; 62% never smoked and 6% were current smokers in the crizotinib arm versus 65% and 3%, respectively, in the chemotherapy arm; 94% had adenocarcinoma in both arms; 98% had metastatic disease in both arms; 94% had ECOG PS 0 or 1 in the crizotinib versus 95% in the chemotherapy arm; and 26% had brain metastases at baseline in crizotinib versus 27% in the chemotherapy arm. There was a median duration of OS follow-up of 17.4 months in the crizotinib arm versus 16.7 months in the chemotherapy arm. For OS, the results favoured crizotinib with a HR of 0.82 (95% CI: 0.54,1.26), which was consistent with the PFS results (HR of 0.45, 95% CI: 0.35, 0.60).

The Cochrane Risk of Bias 2.0 tool[48] was used to critically appraise this RCT. A low risk of bias was assigned for the Randomization Process domain. Some concerns were noted for the Deviations From the Intended Interventions domain such as the lack of blinding, and the permittance of patients to crossover to the crizotinib arm. Of note, the statistical analysis adjusted for this crossover. A low risk of bias was assigned for the Missing Outcome Data, Measurement of the Outcome, and the Selection of the Reported Result domains. Overall, it was concluded that this was a well-conducted trial. More recent estimates of this study were available.[49] However, the sponsor did not provide these updated data to CADTH for incorporation into the PE mode.[28]

Notably, directly using the HR as reported in the PROFILE 1014 trial as the comparative estimate in the sponsor's economic analysis is a major limitation as it is not possible to determine if any observed differences in efficacy between the therapies is solely due to the treatment or, rather, due to bias or confounding factors such as differences in study populations, definitions of outcomes, or study designs. The opposite may also occur where a finding of similar efficacy between treatments may be incorrect because differences in the included trials may have masked true treatment differences.[5] Due to the above limitations, the comparative efficacy estimates obtained should be interpreted with caution as they are likely biased. It is difficult to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with entrectinib compared with pemetrexed-plus-platinum chemotherapy.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Lung Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on entrectinib (Rozlytrek) for ROS-1- positive advanced non-small cell lung cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials December 2019, Embase 1974 to 2020 January 14, Ovid MEDLINE(R) ALL 1946 to January 14, 2020

Search Strategy:

#	Searches	Results
1	(Rozlytrek* or entrectinib* or RXDX101 or RXDX-101 or NMSE628 or NMS E628 or NMS-E-628 or L5ORF0AN1I).ti,ab,ot,kf,kw,hw,nm,rn.	463
2	1 use cctr	10
3	1 use medall	82
4	*entrectinib/	88
5	(Rozlytrek* or entrectinib* or RXDX101 or RXDX-101 or NMSE628 or NMS E628 or NMS-E-628).ti,ab,kw,dq.	304
6	or/4-5	305
7	6 use oemezd	220
8	7 not (conference review or conference abstract).pt.	112
9	3 or 8	194
10	limit 9 to english language	192
11	2 or 10	202
12	remove duplicates from 11	134
13	7 and (conference review or conference abstract).pt.	108
14	limit 13 to english language	108
15	limit 14 to yr="2015 -Current"	101
16	12 or 15	235

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#3	Search #1 AND #2 Filters: English	9
#2	Search publisher[sb]	385,091
#1	Search entrectinib [Supplementary Concept] OR L5ORF0AN1I[rn] OR Rozlytrek*[tiab] OR entrectinib*[tiab] OR RXDX101[tiab] OR RXDX-101[tiab] OR NMSE628[tiab] OR NMS E628[tiab] OR NMS-E-628[tiab]	81

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Rozlytrek/entrectinib, ROS1 positive NSCLC

Select international agencies including:
US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Rozlytrek/entrectinib, ROS1 positive NSCLC

Conference abstracts:
American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/
Search: Rozlytrek/entrectinib, ROS1 positive NSCLC — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the above mentioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[50]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Rozlytrek (entrectinib).

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of November 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[51] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by contacting the CADTH Clinical Guidance Panel to ensure no further studies were potentially relevant. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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