pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the CADTH pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *Procedures for the CADTH pan-Canadian Oncology Drug Review*, which are available on the CADTH website. The Final Recommendation will be posted on the CADTH website once available and will supersede this Initial Recommendation.

Drug: Entrectinib (Rozlytrek)

Submitted Reimbursement Request:
ROZLYTREK (entrectinib) as monotherapy for the first-line treatment of patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer

Submitted by:
Hoffmann-La Roche Ltd.

Manufactured by:
Hoffmann-La Roche Ltd.

NOC Date:
May 5, 2020

Submission Date:
January 8, 2020

Initial Recommendation Issued:
January 8, 2021

Approximate per Patient Drug Costs	Entrectinib costs $95.33 per 200 mg and $48.67 per 100 mg capsule. At the recommended dose of 600 mg administered orally, once daily, entrectinib costs $8,008 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of entrectinib for the first-line treatment of patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- the public drug plan costs of treatment with entrectinib should not exceed the public drug plan costs of the least costly tyrosine kinase inhibitors (TKIs) currently reimbursed for treatment-naive ROS1-positive locally advanced or metastatic NSCLC.

Eligible patients include those with good performance status. Treatment with entrectinib should continue until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that entrectinib may have a net clinical benefit based on clinically meaningful objective response rates (ORRs), intracranial responses in patients with baseline central nervous system (CNS) metastases duration of response (DoR), progression-free survival (PFS), and a manageable toxicity profile. However, pERC acknowledged that, because of the non-randomized, non-comparative study designs of the available clinical evidence, there was considerable uncertainty in the magnitude of clinical benefit of entrectinib. Furthermore, pERC was unable to reach a conclusion on the

	relative efficacy and safety of entrectinib compared with crizotinib, another relevant treatment option. pERC also concluded that entrectinib aligns with the following patient values: delays disease progression, improves disease symptoms, has manageable toxicities, and offers an additional treatment option with a more convenient oral route of administration. pERC concluded that, at the submitted price, entrectinib is unlikely to be cost-effective when compared to standard chemotherapy or crizotinib. Given the lack of direct head-to-head comparative evidence available and the uncertainties introduced by using clinical effectiveness estimates from the sponsor's indirect treatment comparisons, there is insufficient evidence to justify a cost premium over the least expensive TKI reimbursed for the treatment of first-line ROS1-positive locally advanced or metastatic NSCLC. pERC also concluded that the budget impact associated with the uptake of entrectinib at the submitted price would vary depending on the actual population size, the relative duration of therapies, and the market uptake of entrectinib.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there may be a net clinical benefit of entrectinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of entrectinib. pERC noted that a reduction in the price of entrectinib would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted budget impact. **Companion Diagnostic Test (ROS-1 testing)** pERC agreed that timely determination of ROS-1 status is required prior to initiating treatment with entrectinib. The Committee noted that it would be ideal for jurisdictions to have ROS-1 testing results at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation. **Please Note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In Canada, an estimated 29,300 people were diagnosed with lung cancer and an estimated 21,000 deaths from lung cancer in 2019. NSCLC represents approximately 85% of all cases of lung cancer. ROS1 mutations occur in 1% to 2% of NSCLC cases and it is more common in younger, female, and non-smoking patients. It is estimated that there are approximately 200 new cases of ROS1-positive NSCLC per year. Some patients present with early disease and can be cured by surgery. Platinum-based doublet chemotherapy (e.g., cisplatin plus pemetrexed) has been the standard of care for first-line treatment of patients with advanced NSCLC with a median overall survival (OS) that does not exceed one year and response rates of 15% to 30%. In 2019, crizotinib received a positive conditional pERC recommendation as a single agent as first-line treatment for patients with ROS1-positive advanced NSCLC; however, crizotinib is not funded for this indication in all jurisdictions at this time. Thus, pERC agreed with the CADTH Clinical Guidance Panel (CGP), the registered clinicians, and the patient advocacy group providing input for this submission that there is a need for more effective and more tolerable treatment options for this patient population.

pERC's Deliberative Framework for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated the results of an integrated analysis of a pooled subgroup of patients with ROS-1 positive metastatic NSCLC from three non-comparative trials, ALKA-372-001, STARTRK-1, and STARTRK-2. ALKA-372-001 and STARTK-1 were both multi-centre, open-label, single-arm phase I dose escalation studies. STARTRK-2 was a multi-centre, open-label, single-arm, phase II basket study. pERC noted that the reimbursement request was for first-line treatment for patients with ROS1-positive advanced NSCLC which aligned with the pooled subgroup of patients. pERC considered that the integrated analysis included a subgroup of patients who had ROS-1 positive NSCLC and no prior ROS-1 inhibitor treatment (e.g., crizotinib). pERC discussed the evidence from the integrated analysis which demonstrated clinically meaningful ORRs, intracranial response rates among patients with baseline CNS disease, DoR, and PFS. pERC discussed that the integrated analysis demonstrated impressive and clinically meaningful ORRs that appeared substantially greater than expected with historical controls of treatment with platinum-based chemotherapy. However, pERC noted that OS was not estimable in the integrated analysis. pERC also considered the CGP's conclusion and input from registered clinicians that highlighted the clinically meaningful CNS penetration associated with entrectinib and that crizotinib is associated with poor CNS penetration.

pERC deliberated the safety of entrectinib and agreed with the CGP that entrectinib's toxicity profile appears manageable, consistent with other targeted therapies for locally advanced or metastatic NSCLC. pERC noted that data for the overall safety population (regardless of tumour type or gene rearrangement) and the ROS-1 positive NSCLC safety population were overall similar. The most frequent grade 3 or 4 adverse events (AEs) in the overall safety population included anemia, increased weight, dyspnea, and fatigue/asthenia. pERC noted the high proportion of AEs suspected to be drug-related, the majority of which were of grade 1 or 2. The most frequent grade 1 or 2 drug-related AEs in both safety populations included dysgeusia, dizziness, constipation, and diarrhea. pERC noted some patients had nervous system disorders and psychiatric disorders, which may be a side effect of CNS penetration with entrectinib. However, pERC noted that the single-arm, non-randomized design of the integrated data set makes interpreting the safety events attributable to entrectinib challenging, given that all patients received the same treatment.

pERC discussed the available patient-reported outcomes data, which were only collected in the STARTRK-2 trial and were summarised descriptively. pERC discussed the quality of life (QoL) data and noted that baseline global health status/QoL and functional scores showed a trend in improvement while cognitive scores showed worsening. Overall, pERC concluded that it was challenging to interpret the QoL data given the high patient drop-off at later cycles and the lack of direct comparative estimates as all patients in the trials received the same treatment.

pERC acknowledged that due to the non-comparative study designs of the ALKA-372-001, STARTRK-1, and STARTRK-2, there is uncertainty in the magnitude of the clinical benefit of entrectinib in comparison with available therapies, including crizotinib. Nevertheless, pERC acknowledged that the integrated analysis of the three trials demonstrated clinically meaningful ORRs, intracranial response rates among patients with baseline CNS disease, DoR, and PFS. pERC noted that treatment with platinum-based doublet chemotherapy has low response rates and marginal impact on survival. In addition, pERC considered that there are currently no randomized trials underway evaluating entrectinib in patients with ROS1-positive NSCLC. The Committee considered that a randomized controlled trial that compares entrectinib with crizotinib is currently being planned, however, even if successfully completely, would require several years to provide mature data. pERC agreed with the CGP, registered clinician input, and patient input that there is an unmet need for patients with ROS1-positive NSCLC as chemotherapy is only suitable for select patients and immunotherapy is generally not effective for the management of NSCLC with driver mutations. Overall, pERC concluded that there may be a net clinical benefit of treatment with entrectinib based on the clinically meaningful ORR, DoR, PFS, and manageable toxicity profile.

In addition to the integrated analysis, pERC also deliberated the results of submitted indirect treatment comparisons (ITCs) that aimed to estimate the relative effectiveness of entrectinib with other relevant treatments for this patient population. Overall, results suggested that entrectinib was favoured over chemotherapy and entrectinib was similar to crizotinib for the ROS-1 positive NSCLC population. However, pERC acknowledged the limitations of all the ITCs noted by the CADTH Methods Team and agreed with concerns regarding: heterogeneity across the study designs and populations; inability to adjust for all potential confounders and prognostic variables; and use of inappropriate analysis methods for the Matching-Adjusted Indirect Comparison (MAIC). Therefore, pERC agreed with the CGP and CADTH Methods Team's conclusion that there is high uncertainty with respect to the comparative effectiveness of entrectinib to relevant treatment options.

pERC deliberated the patient advocacy group input from one patient group concerning entrectinib. The Committee noted that patients value effective treatments that prolong survival, improve QoL, and have manageable side effects. pERC noted that entrectinib is an oral drug that provides patients the convenience of administering medication at home and would not require frequent visits to a cancer clinic. Fifteen patients and one caregiver had experience with entrectinib. Patient group input indicated entrectinib was able to control the disease including CNS metastases, manage side effects, improve treatment experience due to the oral administration route, allow patients to enjoy life activities, remain independent, return to work, and engage in physical activities. Overall, pERC concluded that it was satisfied that entrectinib aligns with patient values in that it delays disease progression, improves disease symptoms, has manageable toxicities, and offers an additional treatment option with an oral route of administration. However, pERC noted that in some jurisdictions, oral medications are not funded by the same mechanism as intravenous cancer medications.

pERC deliberated the cost-effectiveness of entrectinib compared with crizotinib or pemetrexed plus platinum-based chemotherapy in first-line treatment of patients with treatment-naïve ROS1-positive locally advanced or metastatic NSCLC. pERC discussed that a key limitation was the clinical evidence that informed the economic model. Given the non-randomized, non-comparative study designs of the available clinical evidence, there was considerable uncertainty in the magnitude of clinical benefit associated with entrectinib. Furthermore, in light of the lack of direct comparative clinical evidence and lack of robust indirect evidence, pERC was unable to conclude on the relative efficacy and safety of entrectinib compared with crizotinib. Given these limitations, the magnitude of the life-year and quality-adjusted life-year (QALY) benefit associated with entrectinib were considered highly uncertain. pERC further noted that the results of the cost-effectiveness analysis are sensitive to the uncertainties in the clinical parameters and related assumptions, including: the relative OS benefit for entrectinib compared to crizotinib; the survival model used to extrapolate long-term OS for entrectinib; and, the assumptions regarding treatment waning. pERC considered that there is insufficient evidence to justify a cost premium over the least expensive TKI reimbursed for the treatment of first-line ROS1-positive locally advanced or metastatic NSCLC. pERC noted that if no difference in OS and PFS was assumed between entrectinib compared with crizotinib, entrectinib would be dominated by crizotinib (i.e., entrectinib was associated with the same number of QALYs but was more expensive than crizotinib). pERC therefore concluded that there are uncertainties in the interpretation of economic results and the results should be interpreted with caution given the lack of comparative clinical evidence.

pERC also discussed the budget impact analysis. The expectation is that the availability of a second TKI product would not expand the TKI class market share, and as such, this would limit the predicted budget impact of entrectinib. pERC further noted that the budget impact associated with the uptake of entrectinib at the submitted price would vary depending on the actual population size, the relative duration of therapies, and the market uptake of entrectinib.

The Committee deliberated the input from PAG, regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group: Lung Cancer Canada (LCC)
- Input from registered clinicians: two clinicians on behalf of Cancer Care Ontario (CCO) Lung Drug Advisory Committee (DAC) and six clinicians on behalf of LCC
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of entrectinib (Rozlytrek), compared with standard of care in Canada for the first-line treatment of patients with ROS-1 positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

Studies included: One non-comparative phase I trial and two non-comparative phase II trials

The CADTH systematic review included three trials. ALKA-372-001 was an open-label, single-arm, multi-center phase one dose escalation study examining entrectinib monotherapy administered orally as capsules in the thee dosing schedules until recommended phase II dose (RP2D) determination (doses ranged from 100 mg/m^2 to 1,600 mg/m^2). STARTRK-1 was a multi-centre, open-label, single-arm, phase I dose escalation study examining entrectinib monotherapy dose (capsules taken orally) of 100 mg/m^2 once daily, for 28 consecutive days in repeated four-week cycles (other doses tested: 200 mg/m^2, 400 mg/m^2, or 600 mg or 800 mg once daily). STARTRK-2 was a multi-centre, open-label, single-arm, phase II basket study examining entrectinib monotherapy administered orally as capsules at a dose of 600 mg per day continuously for 28 days (four-week cycles).

An integrated efficacy analysis from a pooled subgroup of patients with locally advanced or metastatic ROS-1 positive NSCLC from the three trials was conducted.

Patient populations: Previously untreated with crizotinib, a proportion of patients with metastatic CNS disease

The Primary ROS-1 positive NSCLC Efficacy-Evaluable Analysis Set was the primary efficacy population for this review which consisted of a pooled subgroup of 53 adult patients at least 18 years of age with locally advanced or metastatic 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 a blinded independent central 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 Performance Status (ECOG PS) of less than or equal to 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 the pooled data set.

The Primary ROS-1 Efficacy Evaluable Analysis Set comprised of 34 (64%) females and 19 (36%) males at baseline. The median age was 53 (range 27 to 73), with a large proportion of patients less than 65 years of age (n = 42; 79.2%). Twenty-three patients (43.4%) 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%). The number of previous systemic therapies received by patients were reported as follows: [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%).

Key efficacy results: Objective response rate; magnitude of comp9arative benefit uncertain
The primary efficacy outcomes for the integrated efficacy set were ORR, best overall response (BOR) and DoR as per BICR assessment. Secondary outcomes were clinical benefit rate (CBR), PFS, time-to-CNS progression, OS, intracranial ORR (IC-ORR), intracranial DoR (IC-DoR), and intracranial PFS (IC-PFS).

For the May 31, 2018 data cut-off date, the median duration of follow-up from the time of first response was 16.6 months (95% confidence interval [CI], 13.8 to 17.9) and the median survival follow-up was 15.5 months (95% CI, 14.8 to 19.0).

Forty-one of the 53 patients achieved a confirmed response (72%). The ORR by BICR was 77% (95% CI, 64% to 88%). The BICR-assessed ORR in patients without baseline CNS metastatic disease was 80% (95% CI, 61% to 92%) (24 patients) and it was 74% (95% CI, 52% to 90%) for patients with baseline CNS disease (17 patients).

For the BOR, a total of three (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, 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.

The BICR DoR among responders was a median of 24.6 months (95% CI: 11.4, 34.8). The DoR was longer for patients with no baseline CNS disease at 24.6 months (95% CI, 11.4 to 34.8) compared to 12.6 months (95% CI, 6.5 to not estimable) for patients with baseline CNS disease.

Eleven of the 20 patients with CNS disease at baseline as determined by BICR experienced an intracranial response (complete response in 20%, four of 20, and partial response in 35%, seven of 20). The Intracranial ORR was 55% (95% CI, 32% to 77%). The intracranial DoR was 12.9 months (95% CI, 5.6 to note estimable).

There were 25 patients (47.2%) who experienced a PFS event and the median PFS was 19.0 months (95% CI, 12.2 to 36.6; 25th percentile: 7.7, 75th percentile: 36.6; range: 0 to 36.6). The PFS event-free rates at six, nine, 12, and 18 months were 80% (95% CI, 68% to 91%), 69% (95% CI, 56% to 82%), 65% (95% CI, 51% to 78%), and 52% (95% CI, 36% to 68%), respectively. Fourteen patients without baseline CNS disease experienced a PFS event and the PFS was a median of 26.3 months (95% CI, 15.7 to 36.6). Eleven patients with baseline CNS disease experienced a PFS event and the PFS was shorter than for those without baseline CNS disease (13.6 months, 95% CI, 4.5 to not estimable). For the 20 patients with CNS disease at baseline, the median intracranial PFS was 7.7 months (95% CI, 3.8 to 19.3).

Nine (17%) patients had died. The median OS was not estimable. The OS event-free rates at six, nine, 12, and 18 months were 92% (95% CI, 84% to 100%), 87% (95% CI, 78% to 97%), 85% (95% CI, 74% to 95%), and 82% (95% CI, 70% to 93%), respectively.

Updated results at the May 1, 2019 data cut-off date were 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 positive NSCLC at the time of May 1, 2019 data cut-off date demonstrated consistency with the results reported for the 53 patients at the time of the May 31, 2018 data cut-off date.

Patient-reported outcomes: Summarized descriptively; no significant detrimental effect on health related quality of life (HRQoL)
HRQoL data were only evaluated in the STARTRK-2 trial and the HRQoL results were overall consistent between the May 31, 2018 and May 1, 2019 data cut-off dates. Due to the small number of patients (n = 37) available at the May 31, 2018 data cut, this section focuses on the results from the May 1, 2019 data cut-off date with 78 patients providing HRQoL data. 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.

The number of patients available to provide patient-reported outcomes data declined steadily over the course of the study and therefore the interpretation of changes from baseline is limited by the high patient drop-off rate 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 that showed worsening scores at most assessment points. For the QLQ-LC13 instrument, patients reported lung symptom burden at baseline with trends toward 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. 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.

HRQoL data were summarized descriptively. The trial was non-randomized and the impact of entrectinib in relation to other therapies is unknown.

Limitations: No comparative data comparing entrectinib with crizotinib; exploratory pooled analysis

ALKA-372-001, STARTRK-1, and STARTRK-2 were single-arm studies and did not include a comparator, which makes it uncertain whether patients will have better or worse outcomes with entrectinib when compared to a relevant comparator. In 2019, crizotinib received a positive conditional pERC recommendation as a single agent as first-line treatment for patients with ROS1-positive advanced NSCLC; however, crizotinib is not funded for this indication in all jurisdictions at this time. Currently, only indirect comparisons can be made between entrectinib and crizotinib. Results based on the sponsor-submitted 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.

The CADTH Methods Team identified severe limitations with the indirect comparisons including concerns regarding heterogeneity across the study designs and populations, inability to adjust for all potential confounders and prognostic variables, and use of inappropriate analysis methods for the MAIC. Therefore, the CGP and CADTH Methods Team concluded that there is high uncertainty with respect to the comparative effectiveness of entrectinib to crizotinib.

The CGP noted that the integrated analysis demonstrated ORRs that appeared greater than expected with historical controls of treatment with platinum-based chemotherapy. Platinum-based chemotherapy (e.g., cisplatin plus pemetrexed) has been the backbone therapy for first-line treatment of patients with advanced NSCLC with a median OS that does not exceed one year and response rates of 15% to 30%.

The results of three trials (ALKA-372-001, STARTRK-1, and STARTRK-2) were pooled to form the ROS-1 positive NSCLC Efficacy Evaluable Analysis Set, which was considered exploratory in nature. The sponsor noted that because of the rare disease setting for ROS-1 positive NSCLC, both the FDA and European Medicines Agency 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.

Safety: Limited evidence suggests tolerable and manageable toxicity

Safety data were presented in two sets:

- Overall Safety Analysis Population (n = 355) (regardless of tumour type or gene rearrangement): comprised of patients from ALKA, STARTRK-1, STARTRK-2, and supplemented with a few patients from one pediatric trial (STARTRK-NG).
- ROS-1 Positive NSCLC Safety Population (n = 134): included adult patients from the three adult trials (ALKA, STARTRK-1, and STARTRK-2).

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.

In the Overall Safety Population (n = 355), 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 grade 3 or 4 AEs. Grade 3 or 4 AEs occurring most frequently included anemia (9%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), pneumonia, pulmonary embolism, hypoxia, and AST increase (each 3.4%), cognitive impairment (4.5%), pleural effusion and aspartate aminotransferase (AST) increase (each 3.1%), hypotension/ orthostatic hypotension and hypophosphatemia (each 2.8%), neutropenia and syncope (each 2.5%), urinary tract infection (UTI) (2.3%), diarrhea, hypokalemia, hyponatremia, and lipase increases (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.

In the n = 133 set, all ROS-1 fusion positive patients (100%) experienced an AE, and 61% experienced a grade 3 or 4 AE. Serious AEs occurred in 37% of patients. A total of 100% of patients experienced a treatment-related AEs. The majority of treatment-related AEs were grade 1 or 2. The most common grade 1 to 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%), AST increase (2%), and alanine aminotransferase increase (2%). There were a few grade 4 treatment-related AEs including hyperuricaemia, blood creatine phosphokinase increase, limbic encephalitis, anorectal disorder and myocarditis (each n = 1, less than 1%). Thirteen percent of patients 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.

Need and burden of illness: Need for more effective therapies for patients with ROS-1 mutations

In Canada, an estimated 29,300 people were diagnosed with lung cancer and an estimated 21,000 deaths from lung cancer in 2019. NSCLC represents approximately 85% of all cases of lung cancer. ROS1 mutations occur in 1-2% of NSCLC cases and it is more common in younger, female, and non-smoking patients. It is estimated that there are approximately 200 new cases of ROS1-positive NSCLC per year. Some patients present with early disease and can be cured by surgery. Platinum-based doublet chemotherapy (e.g., cisplatin plus pemetrexed) has been the standard of care for first-line treatment of patients with advanced NSCLC with a median overall survival (OS) that does not exceed one year and response rates of 15% to 30%. In 2019, crizotinib received a positive conditional pERC recommendation as a single agent as first-line treatment for patients with ROS1-positive advanced NSCLC; however, crizotinib is not funded for this indication in all jurisdictions at this time. The CGP and the registered clinicians providing input agreed that there is a need for more effective and more tolerable treatment options for this patient population.

Registered clinician input: High unmet need for targeted therapies for the ROS-1 mutation

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 CCO Lung 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 positive NSCLC. Chemotherapy is contraindicated in poor performance status patients (e.g., frailer patients, patients with comorbidities, or patients with CNS metastases) while immunotherapy has limited activity in tumours harbouring driver mutations (e.g., ROS-1, epidermal growth factor receptor [EGFR], and anaplastic lymphoma kinase [ALK]) and exhibit a potential for significant autoimmune toxicities. 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 drug. 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 drugs. 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.

PATIENT-BASED VALUES

Experience of patients with ROS-1 positive locally advanced or metastatic NSCLC: Significant physical, emotional financial burden on patients and caregivers

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. Patients reported feeling scared about their health, overwhelmed about treatment options and survival, and worried about their loved ones and the future when diagnosed with lung cancer. LCC highlighted that ROS-1 positive NSCLC patients have limited options in Canada. Crizotinib is the agreed upon standard of care; however, it is not funded in all jurisdictions in Canada at this time and is not affordable. Alternative options include chemotherapy, which is associated with significant side effects and multiple and long trips to the hospital for administration. Because this population of patients tends to be younger, they expressed significant concerns about time taken off work to recover from chemotherapy. Additionally, challenges with handling financial hardships, competing family priorities, and care related to the disease and treatments result in significant physical and psychological burdens for patients and caregivers. Immunotherapy is another option, which has more manageable side effects but has been shown to work poorly in patients with ROS-1 positive NSCLC regardless of programmed death-ligand 1 (PD-L1) status.

Patient values and experience on or expectations for treatment: manageable side-effects; allowed to return to work and resume normal activities

A total of 16 respondents (15 patients and one caregiver) reported having experience with entrectinib for the treatment of ROS-1 positive NSCLC. Entrectinib was reported to control the cancer; elicit manageable side effects; improve treatment experience due to the oral route of administration; and allow patients to enjoy life activities, remain independent, live a new normal life, and for some patients to return to work. Among the 16 responses, 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, patients value more effective and easier, more convenient oral treatment modalities with manageable side effects that keep them progression-free and result in improved symptoms, better QoL and better survival rates.

ECONOMIC EVALUATION

Entrectinib is available as 100 mg and 200 mg capsules at a recommended daily dose of 600 mg until disease progression or no longer tolerated. At the sponsor-submitted price of $48.67 per 100 mg and $95.33 per 200 mg capsule, the 28-day cycle cost is $8,008 per patient.

The sponsor submitted a cost-utility analysis comparing entrectinib with crizotinib or pemetrexed plus platinum-based chemotherapy for its reimbursement requested indication of first-line treatment of patients with treatment-naive ROS1-positive locally advanced or metastatic NSCLC. The sponsor submitted a three-state partitioned survival model with three mutually exclusive states: progression-free, progressed disease, and death. The proportion of patients in each state over the model time horizon was derived directly from OS and PFS curves. Patients were assumed to remain on first-line therapy until disease progression. Three single-arm trials (ALKA-372-001, STARTRK-1, and STARTRK-2) were pooled to inform the efficacy and safety of entrectinib. Efficacy, in the form of OS and PFS, were extrapolated from the pooled data using parametric methods for entrectinib. As there were no head-to-head comparisons to

entrectinib, comparative efficacy of entrectinib relative to crizotinib was derived from a propensity score matching analysis to the US Flatiron community cancer clinic database. The comparative efficacy of entrectinib to chemotherapy was based on the PROFILE 1014 trial, which reported the hazard ratios for chemotherapy relative to crizotinib and was subsequently applied to the adjusted PFS and OS curves for crizotinib. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 10-year time horizon.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The clinical efficacy of entrectinib is uncertain as the available evidence is all from open-label, single-arm, unblinded trials. When pooling, no adjustments were conducted to account for the considerable heterogeneity observed between the studies.
- Comparative clinical efficacy for entrectinib compared with crizotinib or chemotherapy was based on multiple different data sources. Substantial heterogeneity across the study designs and populations, and the omission of important prognostic variables in the propensity scoring method introduced uncertainty in the indirect comparison estimates that were used in the economic analysis. It was therefore considered inappropriate to perform and interpret the results sequentially.
- Extrapolated OS for entrectinib was overestimated in the sponsor's model as it does not align with the observed survival expected for this patient population according to the clinical experts consulted.
- The sponsor overestimated the proportion of patients receiving a TKI as subsequent treatment after entrectinib or crizotinib; consequently, increasing subsequent treatment costs.
- The sponsor did not include the cost of ROS-1 testing. As ROS-1 testing is not routinely available, the introduction of entrectinib is expected to be associated with an increase in testing costs.

Given the inconclusiveness of the comparative clinical evidence, the cost-effectiveness of entrectinib is highly uncertain. CADTH undertook exploratory reanalyses to correct the sponsor's model using the best available evidence, but the validity and interpretability of the results are limited by the comparative evidence. If no difference in OS and PFS is assumed between entrectinib compared with crizotinib, entrectinib would be dominated by crizotinib (i.e., entrectinib is more costly and equally effective). Sensitivity analyses demonstrated that the economic model was sensitive to the assumed OS benefit for entrectinib relative to crizotinib; the survival models used to extrapolate the long-term OS for entrectinib; and the assumptions surrounding treatment waning. The modelled population within the economic analysis focused on treatment-naive ROS1-positive locally advanced or metastatic NSCLC patients. Uncertainty remains regarding the cost-effectiveness and budget impact of entrectinib in the full Health Canada indication.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated
CADTH reanalysis suggests that the sponsor-submitted budget impact of introducing entrectinib to the market is underestimated, with the three-year budget impact from the CADTH reanalysis estimated at $2,635,483.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of Entrectinib (Rozlytrek) for ROS-1 positive non-small cell lung cancer (NSCLC), through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group, registered clinicians, and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR guidance reports for more detail on their content.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and

opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
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 harbour 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.	pERC agreed with the CGP that for patients with known 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, then pembrolizumab in combination with chemotherapy or pembrolizumab alone may be offered.
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. A small number of patients in clinical practice have ECOG PS of greater than 2. The CGP noted that it would be reasonable to generalize 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 or ECOG 3 group. pERC noted that it would be reasonable to offer entrectinib to patients with ECOG PS of 2 or greater in patients whose ECOG PS may be related to the underlying disease or tumour symptoms.
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.	pERC agreed with the CGP 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, or single agent immunotherapy (pembrolizumab monotherapy) and have not progressed and to fund patients at any line of therapy if they have not received a ROS-1 targeted treatment.

	However, pERC agreed with the CGP that there is insufficient evidence to ascertain the treatment effect of entrectinib in patients who have started treatment with crizotinib and have not progressed. Furthermore, pERC 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 locally 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 therapy should the recommendation align with the sponsor-requested criteria.	• 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 locally advanced or metastatic disease. The most commonly received anti-cancer therapy was chemotherapy. pERC agreed that entrectinib should be available on a time-limited basis for all patients with ROS-1 positive locally advanced or metastatic NSCLC not previously treated with a ROS-1 targeted therapy, such as crizotinib (unless the patient is experiencing intolerable toxicity from crizotinib).
• 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.	• 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), pERC agreed with the CGP that there is insufficient data to support the generalizability of treatment benefit with entrectinib to patients with other mutations than ROS-1. pERC also agreed with the CGP that the treatment effect of entrectinib cannot be generalized to the adjuvant setting, as entrectinib has not been studied in this setting.
Implementation factors	
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.	In agreement with the CGP, pERC did not anticipate that compared to crizotinib, 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 the 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 positive NSCLC:	
• Is entrectinib the preferred first-line drug 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. The results based on the sponsor-submitted 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 sponsor-submitted propensity score matched comparison

	analysis suggested a difference in OS, PFS, and time to treatment discontinuation favouring entrectinib over crizotinib. However, pERC agreed with the CGP and the CADTH Methods Team, that due to severe limitations identified in the MAIC and propensity score analysis, 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 which of the drugs (i.e., entrectinib or crizotinib) is superior. Therefore, pERC agreed with the CGP that patient values and preferences, comorbidities, 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 positive 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 ORR by BICR was seen in approximately half of the patients with CNS metastases at baseline. In agreement with the CGP, pERC 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.
• Is there evidence to inform use of entrectinib in patients with ROS-1 positive NSCLC who experience CNS disease progression on first-line crizotinib?	• pERC agreed with the CGP that there is a pharmacokinetic advantage for entrectinib in terms of CNS penetration. However, there is currently insufficient evidence to guide a recommendation on the use of entrectinib in patients with ROS-1 positive NSCLC who experience CNS disease progression on first-line crizotinib.
• Can entrectinib be used when a ROS-1 positive tumour acquires a mutation conferring resistance to crizotinib, or vice versa?	• pERC agreed with the CGP 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.
• PAG is seeking confirmation that patients who started chemotherapy, or PD-1 inhibitors while waiting for ROS-1 test results be switched to entrectinib if the results are positive.	• pERC agreed with the CGP that targeted therapy is regarded as superior to chemotherapy, single drug immunotherapy, or chemotherapy-immunotherapy combination in this setting. pERC agreed with the CGP that patients who started chemotherapy, single drug immunotherapy, or chemotherapy-immunotherapy combination while waiting for ROS-1 test results, should be switched to entrectinib if the results are positive.
• PAG is 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?	• pERC was unable to make an informed recommendation on the optimal sequencing of available treatments following progression on first-line treatment with entrectinib. pERC noted that it did not review evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of entrectinib and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Companion Diagnostic Testing	
PAG noted that ROS-1 testing 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	• pERC noted concerns related to the turnaround time for ROS-1 testing. The CGP noted that NGS multiplex testing is becoming more common, with turn around times of one week to 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, pERC and 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)	• pERC agreed with the CGP 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 a 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.	• pERC agreed with the CGP 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 tumour samples.

ALK = anaplastic lymphoma kinase, BICR = blinded independent central review, CGP = Clinical Guidance Panel, CNS = central nervous system, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridization, IHC = immunohistochemistry, 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.