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 pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

**Drug:** Crizotinib (Xalkori)

**Submitted Reimbursement Request:** As a single agent as first-line treatment for patients with ROS1-positive advanced non-small cell lung cancer (NSCLC)

**Submitted by:** Cancer Care Ontario Lung Cancer Drug Advisory Committee

**Manufactured by:** Pfizer Inc.

**NOC Date:** August 28, 2017

**Submission Date:** October 30, 2018

**Initial Recommendation Issued:** May 3, 2019

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| **Approximate per Patient Drug Costs, per Month (28 day cycle)** | • Crizotinib costs $0.52 per mg<br>• At a daily dose of 500 mg, the cost per day is $260.00<br>• The cost per 28 day cycle is $7,280.00 |

**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 recommends the reimbursement of crizotinib (Xalkori) as a single agent as first-line treatment for patients with ROS1-positive non-small cell lung cancer (NSCLC), only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed.

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

pERC made this recommendation because the Committee considered that there is a net clinical benefit of crizotinib based on the clinically meaningful duration of response, progression-free survival (PFS), and overall survival (OS). pERC also considered that there is a significant unmet need for patients with ROS1-positive NSCLC as there are limited effective treatment options available.

pERC concluded that crizotinib aligns with the following patient values: it offers the potential for disease control, delays progression, and prolongs survival with manageable side effects. Crizotinib also addresses the need for an effective oral treatment option to delay treatment with chemotherapy.

pERC noted that at the submitted price, crizotinib is not cost-effective compared with chemotherapy and would require a substantial price

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| | reduction to improve the cost-effectiveness to an acceptable level. Additionally, there is a high level of uncertainty in the cost-effectiveness estimates because of the lack of available direct comparative effectiveness data to inform the submitted economic evaluation. pERC also highlighted that the potential budget impact of crizotinib for patients with ROS1-positive NSCLC is likely underestimated and will be substantial. |
| POTENTIAL NEXT STEPS FOR STAKEHOLDERS | **Pricing Arrangements of Crizotinib to Improve Cost-Effectiveness and Budget Impact**<br>Given that pERC was satisfied that there is a net clinical benefit of crizotinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and the affordability (budget impact) to an acceptable level. pERC noted that the budget impact of crizotinib results from the high cost of crizotinib, market share, and number of eligible patients. pERC concluded that a substantial reduction in drug price would be required to improve the cost-effectiveness and affordability.<br><br>**Time-Limited Need for Crizotinib for Patients With ROS1-Positive NSCLC Who are Currently Receiving Other Therapies or Who Have Been Treated With Other Therapies**<br>At the time of implementing a reimbursement recommendation for crizotinib, jurisdictions may consider addressing the time-limited need of crizotinib for patients with ROS1-positive NSCLC who are currently receiving first-line chemotherapy and for patients who have previously been treated with other therapies (e.g., chemotherapy, PD-1 inhibitors). pERC noted that this time-limited access should be for patients who would otherwise meet the reimbursement criteria.<br><br>**Accessibility and Feasibility of Companion Diagnostic Test**<br>pERC recognized that ROS1 testing is currently not part of standard of care. pERC discussed that ROS1 testing using a validated test authorized by Health Canada or one that is equivalent to that used in the PROFILE 1001 and Ox Onc trials is reasonable. The Committee noted that jurisdictions will need to have validated and reliable ROS1 testing available to identify both the relevant patient population and to manage the budget impact. Evidence generation from jurisdictions would be of value in regards to actual numbers of eligible patients to assess the true budget impact.<br><br>**Sequencing of Crizotinib and Other Available Therapies**<br>pERC noted that there is currently no clinical trial evidence to inform the sequencing of crizotinib and other available treatments for ROS1-positive NSCLC and therefore, optimal sequencing is unknown. Upon implementation of the reimbursement of crizotinib, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing and collection of shared outcomes would be of value.<br><br>**Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and Cost-Effectiveness**<br>Given the considerable uncertainty in the magnitude of clinical benefit of crizotinib in patients with ROS1-positive NSCLC, pERC concluded that the collection of additional prospective evidence to better inform the true clinical benefit and cost-effectiveness of crizotinib would be of value.<br><br>**Please note:** Provincial Advisory Group questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1. |

# SUMMARY OF pERC DELIBERATIONS

In 2017, there were approximately 28,600 new cases of lung cancer and 21,800 deaths from lung cancer. Approximately 85% of these cases are classified as NSCLC. ROS1 mutations occur in 1% of NSCLC cases and it is more common in younger, female, non-smoking patients. It is estimated that there are approximately 250 new cases of ROS1-positive NSCLC per year. Some patients present with early disease and can be cured by surgery. Standard treatment for patients with metastatic ROS1-positive NSCLC is cytotoxic chemotherapy, which has a low response rate of 15% to 30% and marginal impact on median OS. New treatments in the first-line metastatic setting include targeted therapies that have led to improved outcomes in patients with driver mutations, including EGFR and ALK gene rearrangements. However, for the ROS1 mutation, there are no publicly reimbursed targeted therapies available. Thus, pERC concluded that there is a significant 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:

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

pERC deliberated on the results of two non-comparative non-randomized trials, PROFILE 1001 and Ox Onc, that evaluated crizotinib in patients with metastatic ROS1-positive NSCLC. The PROFILE 1001 trial was an open-label, international, multi-centre phase I dose-escalation study of patients ALK-positive NSCLC that was amended to include patients with ROS1-positive NSCLC. The Ox Onc trial was a phase II open-label trial that enrolled Asian patients with ROS1-positive NSCLC who received three or fewer prior lines of systemic therapies. pERC noted that the reimbursement request was for first-line treatment for patients with ROS1-positive advanced NSCLC. pERC considered that the majority of patients in both trials had received at least one prior line of treatment and that there was only a small number of treatment-naive patients enrolled in either trial. pERC discussed that the PROFILE 1001 and Ox Onc trials demonstrated very impressive and clinically meaningful overall response rates (ORR) and PFS in patients who received treatment with crizotinib. Furthermore, pERC noted that in the small subgroup of patients in the PROFILE trial who did not receive previous therapy for advanced disease, the ORR was higher than the ORR for the overall trial population. The Committee also discussed there was long-term follow-up and that the median OS was reached in both trials and appeared substantially longer than expected with historical controls.

The Committee discussed the Clinical Guidance Panel (CGP)'s conclusions regarding the generalizability of treatment with crizotinib in particular subgroups of patients. pERC agreed with the CGP's expert opinion and concluded that patients with a good performance status should be eligible for treatment with crizotinib. pERC also agreed with the CGP that patients with stable brain metastases were enrolled in the trials and that these patients could potentially derive benefit from treatment with crizotinib.

pERC discussed the safety profile of crizotinib and noted that the most common grade 3 and 4 adverse events (AEs) observed in both trials were neutropenia and elevated liver enzymes. The Committee also noted that there was a high number of transient visual impairments reported in both trials. While the Committee noted that these AEs could have an impact on a patient's functioning, the Committee concluded that the side effects of crizotinib could be effectively managed with dose reductions. Additionally, pERC noted that quality of life (QoL) data were collected in the Ox Onc trial. pERC discussed that QoL was considered an exploratory outcome and was collected during the first 20 cycles of treatment. pERC concluded that while there were clinically meaningful improvements observed in QoL, it was challenging to interpret the QoL data given the lack of direct comparative estimates as all patients in the trial received the same treatment.

pERC also considered input from registered clinicians and discussed clinicians' real-world experience in treating patients with ROS1-positive NSCLC with crizotinib. pERC considered that the registered clinicians observed durable responses similar to those reported in the trials, as well as improved QoL and well-being in patients who had been treated with crizotinib. The Committee also acknowledged that registered clinicians noted that treatment with crizotinib can be associated with the ability for patients with ROS1-positive NSCLC, who are typically younger, to return to work or family responsibilities.

pERC acknowledged that due to the non-comparative study designs of the PROFILE 1001 and the Ox Onc trials, there is uncertainty in the magnitude of the clinical benefit of crizotinib in comparison with available therapies, including chemotherapy. Nevertheless, pERC acknowledged that the long-term follow-up in both trials demonstrated a clinically meaningful durable response, delay of progression, and improvement in OS. pERC also considered that treatment with chemotherapy has low response rates and marginal impact on OS. In addition, pERC considered that there are currently no randomized trials underway evaluating crizotinib in patients with ROS1-positive NSCLC. pERC also agreed with the CGP and patient input that despite the significant unmet need in this patient population, conducting a randomized controlled trial that compares crizotinib with chemotherapy would likely not be feasible. The Committee also agreed that there are limited options available for patients with ROS1-positive NSCLC. Overall, pERC concluded that there is a net clinical benefit of treatment with crizotinib based on the clinically meaningful ORR, PFS, OS, and manageable toxicity profile. Given the uncertainty in the magnitude of clinical benefit of crizotinib in patients with ROS1-positive NSCLC, pERC concluded that prospective evidence should be collected to better estimate the magnitude of clinical benefit of crizotinib in patients with ROS1-positive NSCLC.

pERC deliberated on input from two patient advocacy groups concerning crizotinib. The Committee noted that patients value effective treatments that prolong survival, improve QoL, and have manageable side effects. pERC considered that patients attributed enhanced QoL to independence and ease of administering treatment at home. pERC noted that crizotinib is an oral drug that provides patients the convenience of administering medication at home and would not require frequent visits to the cancer clinic. Crizotinib also reduces the burden on caregivers as there was a greater sense of independence among patients who were able to continue being employed, care for their families, and engage in physical activities. pERC also discussed that treatment with crizotinib delays progression and would delay subsequent treatment with chemotherapy for patients The Committee expressed that they were impressed with the patient input which included a number of patients with ROS1 positive NSCLC and caregivers from 32 countries who supported the use of crizotinib. pERC discussed that direct input from a large number of patients and caregivers who had experience with crizotinib, with similar outcomes to the trials, was compelling. Overall, pERC concluded that it was satisfied that crizotinib aligns with patient values in that it is an effective oral treatment option that offers disease control, prolonged PFS and OS, and has a manageable toxicity profile.

pERC deliberated the cost-effectiveness of crizotinib compared with chemotherapy based on the submitted economic evaluation and the reanalysis provided by the pCODR Economic Guidance Panel. The Committee noted that the economic analysis was informed by pooled efficacy estimates for crizotinib and chemotherapy from non-randomized and retrospective studies. pERC noted that the Economic Guidance Panel's lower bound estimate of the incremental cost-effectiveness ratio (ICER) was considered not cost-effective and that an upper bound ICER could not be estimated due to the lack of available direct comparative effectiveness data to inform the economic analysis. pERC acknowledged that because of the non-comparative trial design and the considerable limitations in the pooled analysis informing the comparative efficacy of crizotinib and chemotherapy, there is considerable uncertainty in the magnitude of benefit and therefore considerable uncertainty in the incremental cost-effectiveness of crizotinib. The Committee noted that the factor that most influences the incremental cost is the source of PFS data and the factor that most influenced the incremental clinical effect is the median PFS for second-line treatment for patients receiving crizotinib. In addition, pERC also considered that the economic analysis assumes that patients will be tested upfront for the ROS1-positive mutation and that the cost per case detected is high. The Committee noted that the true ICER is uncertain, and may be underestimated, because the impact of the possible need for repeat biopsies was not explored in the economic analysis, although it could be significant. pERC concluded that at the submitted price, crizotinib is not cost-effective compared with chemotherapy and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level.

pERC discussed factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for crizotinib for the treatment of first-line ROS1-positive NSCLC. The Committee discussed that crizotinib is administered orally and would not require chemotherapy chair time, which pERC considered an enabler to implementation. However, pERC also noted that in some jurisdictions, oral medications are not reimbursed in the same mechanism as intravenous cancer medication which may limit access to crizotinib. pERC noted that ROS1 testing is not routinely available in all provinces and that access to and the cost of ROS1-testing will be a barrier to implementation. pERC agreed that ROS1 testing using a validated test authorized by Health Canada or one that is equivalent to that used in the PROFILE 1001 and Ox Onc trials is reasonable. Additionally, pERC also noted that there

may not be enough tissue sample to test for ROS1 if testing becomes part of upfront testing, which pERC considered to be another barrier to implementation.

pERC also discussed the Provincial Advisory Group's request for information and clarification on the treatment criteria for crizotinib. pERC noted the registered clinicians' and the CGP's expert opinion that the ROS1 mutation is mutually exclusive of other driver mutations. In addition, pERC discussed that there is currently no clinical trial evidence to inform the sequencing of crizotinib and other available treatments for ROS1-positive NSCLC. However, pERC noted that registered clinicians suggested that patients would receive crizotinib as first-line treatment followed by next-generation inhibitors (another targeted therapy) if disease progression occurs. However, pERC noted that there are no other targeted therapies for patients with ROS1-positive NSCLC currently available. If a patient progresses on ROS1-targeted therapy, patients would be treated with platinum doublet chemotherapy. The Committee also noted that registered clinicians and the CGP indicated that immunotherapy with PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab) would be typically reserved for the later lines of therapy, given the lower response rates observed. pERC questioned the use of immunotherapy in later lines of therapy in patients with driver mutations if responses rates are low, particularly given the high cost of this type of treatment. Finally, the Committee recognized that there will be a time-limited need for crizotinib for patients with ROS1-positive NSCLC who are currently receiving first-line chemotherapy or have been previously treated with chemotherapy or immunotherapy.

pERC discussed the submitted budget impact results and noted that the budget impact analysis results provided were for Ontario only. pERC noted the factors that most influence the budget impact include the cost of crizotinib, the number of eligible patients with ROS1-positive NSCLC, and the estimated market share. pERC noted that the cost of testing will need to be considered as part of the budget and that the potential budget impact of crizotinib is likely underestimated and would be substantial.

# 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 submitter's economic model and budget impact analysis (BIA)
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy group(s), Lung Cancer Canada and Ontario Lung Association
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of crizotinib as a single agent for first-line treatment for patients with ROS1-positive advanced non-small cell lung cancer (NSCLC).

### Studies included: One non-comparative phase I trial and one non-comparative phase II trial

The pCODR systematic review included two non-randomized, non-comparative clinical trials, PROFILE 1001 and Ox Onc.

PROFILE 1001 was an open-label, multi-centre phase I dose-escalation, safety, pharmacokinetic and pharmacodynamics study that was conducted in Australia, South Korea, and the US. The study was originally designed to include an initial dose-escalation phase, followed by an expansion phase, with the maximum dose in molecularly defined cohorts of study participants (e.g., ALK-positive expansion cohort). The trial was later amended to include advanced NSCLC patients with tumours having an ROS1 gene translocation. Crizotinib was administered orally at 250 mg twice daily in continuous 28-day cycles until disease progression, unacceptable toxicities, and withdrawal from the study, or death. Patients with disease progression could continue to receive crizotinib at the investigator's discretion. The ROS1 rearrangement was identified using FISH and reverse-transcriptase-polymerase-chain reaction (RT-PCR) assay.

Ox Onc was an open-label, phase II, single-arm study that enrolled East Asian patients with ROS1-positive advanced NSCLC who received three or fewer prior lines of systemic therapies. The trial was conducted in 37 sites in Asia in China, Japan, South Korea, and Taiwan. The ROS1 rearrangement was identified using FISH or RT-PCR assay.

The pCODR review also provided contextual information on an observational study, EUROS1, provided by the submitter. In the absence of comparative efficacy evidence, data from this study was pooled with those from the PROFILE 1001 and Ox Onc trials to inform the economic model.

### Patient populations: Majority of patients received more than one line of treatment prior to crizotinib

Eligibility for the PROFILE 1001 ROS1 expansion cohort included a histologically confirmed advanced NSCLC with ROS1 rearrangement, an Eastern Cooperative Oncology Group performance score of 0 to 2, measurable disease according to RECIST (version 1.0), and adequate organ function. Eligibility for the Ox Onc trial included a histologically or cytologically confirmed locally advanced or metastatic NSCLC with ROS1 rearrangement and negative for ALK rearrangement, an Eastern Cooperative Oncology Group performance score of 0 or 1, three or fewer prior systemic therapies for advanced-stage disease, one or more measurable tumour lesions according to RECIST (version 1.1), and no previous radiation therapy. Patients with brain metastases were eligible if asymptomatic or were neurologically stable for two or more weeks (if treated). Those who had received prior therapies with an activity against ALK or ROS1 mutations were not permitted.

In PROFILE 1001, a total of 53 eligible patients with ROS1-positive NSCLC were enrolled. The median age for the ROS1 expansion cohort was 55 years (range: 25 to 81). The majority of patients were white (56.6%) or Asian (39.6%), and never smokers (75.5%). All patients presented with measurable disease; 96.2% had

adenocarcinoma histology; and 86.8% had received at least one prior line of treatment. In Ox Onc, a total of 127 eligible patients with ROS1-positive NSCLC were enrolled and received one or more doses of crizotinib. All study participants were Asian (58.3% from China, 20.5% from Japan, and the remaining 21.2% from South Korea and Taiwan). The median age was 51.5 years (range: 23 to 80); the majority of patients were never smokers (71.7%), had adenocarcinoma histology (97.6%), had metastatic disease (95.3%), and had received at least one prior line of treatment (81.1%).

### Key efficacy results: Objective response rate; magnitude of comparative benefit uncertain

The key efficacy outcome deliberated on by pERC included the primary end point of overall response rate (ORR) and secondary outcomes including duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

PROFILE 1001: As of the November 30, 2014, data cut-off date, after a median follow-up of 25.4 months, the ORR was 70% (95% confidence interval [CI], 56 to 82), including five (9.4%) patients with complete response, 32 (60.4%) patients with a partial response, and 11 (20.8%) patients with stable disease. The median DOR was 17.6 months (range: 2.8 to 18.1). In the subgroup of seven patients with no prior advanced/metastatic therapies, the ORR was estimated to be 85.7% (95% CI, 42.1 to 99.6).

The median PFS was 19.3 months (95% CI, 14.8 to not reached). The six-month and 12-month OS rates were 91% (95% CI, 79% to 96%) and 79% (95% CI, 65% to 88%), respectively. The median OS was not reached. At an updated analysis on June 30, 2018, after a median follow-up period of 63 months, a total of 26 patients (49.1%) had died. The median OS was 51 months (95% CI, 29 to not estimable), with the OS probabilities at 12, 24, and 48 months being 78.8%, 67.0%, and 50.7%, respectively. The final analysis date was not reported.

Ox Onc trial: As of July 30 2016 data cut-off date, after a median follow-up of 21.4 months, the ORR was 71.7% (95% CI, 63.0% to 79.3%), including 17 (13.4%) patients with a complete response, 74 (58.3%) patients with a partial response, and 21 (16.5%) patients with stable disease. ORR results were not available for the subgroup of treatment-naive patients.

The median DOR was 19.7 months (95% CI, 14.1 to not reached). The median PFS was 15.9 months (95% CI, 12.9 to 24.0). The median OS was 32.5 months (95% CI, 32.5 to not reached). The six-month and 12-month OS rates were 92.0% (95% CI, 85.7% to 95.6%) and 83.1% (95% CI, 75.2% to 88.6%), respectively. The final analysis date was not reported.

### Patient-reported outcomes: Exploratory outcome; improvement in quality of life observed

Patient-reported outcomes (PROs) were not measured in the PROFILE 1001 trial but were measured in the Ox Onc trial. PROs considered exploratory as the trial was not powered to detect statistically significant differences from the baseline in PROs. PROs were reported over the first 20 cycles in the Ox Onc trial. Improvements in global quality of life were statistically significant at cycles 3 to 5, 7, and 10. There were clinically meaningful improvements (defined as greater than 10 points changed) in patient-reported European Organisation for Research and Treatment of Cancer (EORTC) QLQC30 scores for insomnia and dyspnea symptoms at several time points. Additionally, clinically meaningful improvements were observed in EORTC Quality of Life Questionnaire Lung Cancer Module scores for patient-reported symptoms of cough and pain in chest at several time points. A statistically significant and clinically meaningful deterioration from baseline was reported for constipation and diarrhea at multiple time points.

### Limitations: No comparative data comparing crizotinib with available therapies

PROFILE 1001 and Ox Onc were single-arm studies with no active treatment or placebo control groups. As a result, a direct comparison of the efficacy and safety of crizotinib relative to comparators such as chemotherapy is not possible. Of note, no indirect treatment comparisons comparing crizotinib with potentially relevant comparators were provided by the submitter. Both trials are subject to bias when it comes to the analysis of data from patients who did not receive a prior systemic therapy (i.e., the requested reimbursement request), due to the small number of treatment-naive patients in the included trials, with no subgroup analysis results available from the Ox Onc trial for treatment-naive patients. The majority of study participants in the PROFILE and Ox Onc trials had received one or more prior regimen(s).

### Safety: Limited evidence suggests tolerable and manageable toxicity

PROFILE 1001: At the April 11, 2014, data cut-off date, the median duration of treatment was 64.5 weeks (range: 2.3 to 182). The most common adverse events (AEs) reported were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), an elevated aspartate aminotransferase level (22%), fatigue (20%), dysguesia (18%), and dizziness (16%).The most frequently reported treatment-related grade 3 AEs in the PROFILE 1001 trial included hypophosphatemia (10%), neutropenia (10%), and an elevated alanine aminotransferase level (4%). No grade 4 or 5 treatment-related AEs were reported. One patient (2%) discontinued crizotinib due to treatment-related nausea. Five patients died, all due to disease progression. The deaths were considered to be unrelated to the treatment. As of the June 30, 2018, data cut-off date, after a 22-month (95% CI, 15 to 36) median duration of treatment, no new safety signals were noted. The most common grade 3 treatment-related AEs (reported in 5% or more of patients) included hypophosphatemia (15.1%) and neutropenia (9.4%). No grade 4 treatment-related AEs were reported. During the longer-term follow-up, no new death events or withdrawals due to AEs were reported.

Ox Onc: As of the July 30, 2016, data cut-off date, the median duration of crizotinib treatment was 18.4 months (range: 0.1 to 34.1) in the Ox Onc trial. Treatment-related AEs occurred in 96.1% of patients. The most frequently reported treatment-related AEs of any grade included elevated transaminases (55.1%), vision disorder (48.0%), nausea (40.9%), diarrhea (38.6%), and vomiting (32.3%). Grade 3 or 4 treatment-related AEs were reported in 25.2% of patients. The most common grade 3 or 4 treatment-related AEs were neutropenia (10.2%) and elevated transaminases (5.5%). Thirty-nine patients (30.7%) died during the study. Disease progression was the most common cause of death that occurred in 35 patients (27.6%). Other causes of death included: pneumonia in two patients (1.6%), respiratory failure in one patient (0.8%), and unknown in one patient (0.8%). No crizotinib-related deaths were reported.

### Need and burden of illness: Need for more effective therapies for patients with ROS1 mutations

ROS1 mutations occur in one per cent of NSCLC patients and are more common in younger non-smoking patients. It is estimated that there are approximately 250 new cases of ROS1-positive NSCLC per year. Some patients would present with early disease and be cured by surgery. Standard treatment for patients with advanced ROS1-positive NSCLC is chemotherapy, which has a marginal impact on median OS. New treatments in the first-line metastatic setting include targeted therapies that have led to improved outcomes in patients with driver mutations, including EGFR mutated and ALK gene rearrangements. However, for the ROS1 mutation, there are no publicly reimbursed targeted therapies available. Thus, there is a need for more effective treatment options for this patient population.

### Registered clinician input: Crizotinib is superior to chemotherapy for first-line treatment

A group comprised of 17 clinicians provided one joint submission. Crizotinib was stated to be the preferred first-line treatment option for patients with ROS1 mutations, with benefits being superior to chemotherapy. Platinum-based doublet chemotherapy was stated to be the second-line treatment option following ROS1-directed therapy. For patients whose ROS1 status is discovered during or post first-line systemic therapy, crizotinib could also be considered as a second-line treatment option. Clinician input stated that PD-1 or PD-L1 inhibitors do not show the same efficacy among patients with ROS1 mutations, who are predominantly younger and never smoking, compared with smoking populations; therefore, the use of these treatments is expected to be reserved for later lines of therapy in patients who are ROS1 positive. The group of clinicians had experience treating a total 13 patients with ROS1 mutations with crizotinib and found that responses to crizotinib were durable and resulted in improved QoL.

## PATIENT-BASED VALUES

### Experience of patients with ROS1-positive NSCLC: Unmet need for patients who are ROS1 positive

Patient input was received from two patient advocacy groups, Ontario Lung Association and Lung Cancer Canada. Both patient groups noted the stress patients and caregivers feel due to the diagnosis of lung cancer. Patient input noted that symptoms of lung cancer have an impact on the independence of patients, including their ability to work, travel, and participate in physical activity.

Patient input reported that the current standard therapy for patients is chemotherapy and that side effects with this therapy include nausea, vomiting, and extreme fatigue. Patient input also emphasized

the negative impact of both lung cancer and treatment on family life, and because ROS1-positive NSCLC tend to be female and younger than the average lung cancer patient, patients are more likely to have dependent children to take care of.

### Patient values on treatment: Effective treatment with manageable side effects and better quality of life

Patient input indicated that patients value effective treatments that prolong survival, improve QoL, and have manageable side effects. Patients valued the ease of administering treatment at home and considered that this would improve their QoL. Crizotinib is an oral drug that provides patients the convenience of administering medication at home and would not require frequent visits to the cancer clinic. The patient input included 259 patients who were ROS1 positive and caregivers from 32 countries who supported the use of crizotinib. Overall, from the perspectives of patients with ROS1-positive NSCLC, they value a chance to extend their life and spend more time with their families by having a treatment that is effective, and improves their symptoms and outcomes.

## ECONOMIC EVALUATION

### Economic model submitted: Cost-effectiveness and cost-utility analysis

The economic analysis compared crizotinib with standard of care for first-line treatment of previously untreated patients with ROS1-positive advanced NSCLC. Standard of care was defined as platinum doublet chemotherapy (cisplatin or carboplatin and pemetrexed). The majority of patients had received at least one prior line of treatment and there was a small number of treatment-naive patients.

### Basis of the economic model: Markov model comprised of five health states

The economic model was comprised of five health states: PFS (first-line treatment), progression (second-line treatment), progression (third-line treatment), palliation, and death.

Only patients who test positive for ROS1 enter the model in the progression-free state; health states are mutually exclusive. Patients may progress on up to two additional lines of treatment, which are administered until further progression. Patients deemed unfit for additional treatment enter the palliation state.

Pooled efficacy estimates for crizotinib and chemotherapy were obtained from non-randomized and retrospective studies. In addition to the data provided from ROS1-positive studies, the submitter provided a scenario analysis using untreated ALK-positive advanced NSCLC data as a proxy for this reimbursement request. The Economic Guidance Panel (EGP) did not consider this data as the Clinical Guidance Panel confirmed that the populations are different and that using the patient population of those who are ROS1 positive was more appropriate than a proxy population of patients who are ALK positive.

Costs considered include molecular testing for ROS1, drug costs, subsequent treatment drug costs, drug administration costs, monitoring costs, AE costs, and palliative care costs.

### Drug costs: High cost of crizotinib

Crizotinib costs $0.52 per mg. At a daily dose of 500 mg, the cost per day is $260.00. The cost per one-month cycle is $7,280.00.

Carboplatin costs $0.10 per mg. At an assumed dose of $567.20 mg per cycle, the monthly drug cost is $82.21.

Cisplatin costs $0.23 per mg. At an assumed dose of 75 mg/m$^2$ per cycle, the monthly drug cost is $45.81.

Pemetrexed maintenance costs $0.21/mg/m$^2$. At an assumed dose of 500 mg/m$^2$, for a 21-day cycle, the drug cost is $279.81 (both induction and maintenance).

### Clinical effect estimates: Considerable uncertainty in the comparative effectiveness data

There is no head-to-head clinical trial of crizotinib versus chemotherapy for the treatment of ROS1-positive NSCLC, nor was there sufficient evidence to perform an indirect treatment comparison. Given the small sample size of identified individual studies (notable in the chemotherapy arm), and the range of

outcomes reported, there was no single study for either treatment arm that emerged as the most appropriate source of efficacy. As such, a pooled analysis of time-to-event data of all identified studies was included. However, none of the studies included were randomized controlled trials. It is difficult to estimate the impact of this on the incremental cost-effectiveness ratio (ICER), as it is unknown what the magnitude of the effect would be in a trial comparing crizotinib with chemotherapy.

### Cost-effectiveness estimates: Not cost-effective at the submitted price

The EGP's lower bound ICER estimate was higher ($314,854 per quality-adjusted life-year) than the submitter's best estimate ($273,286 per quality-adjusted life-year). The EGP's upper bound ICER is not estimable due to the uncertainty and lack of available direct comparative effectiveness data.

The EGP's best estimate of the lower bound ICER was based on the following assumptions that were supported by the Clinical Guidance Panel: a shorter median PFS of 4.2 months for second-line treatment following progression in the crizotinib arm, lower utilities based on PROFILE 1014 for both treatment arms in the PFS state, and a smaller proportion (30%) of patients receiving active therapy in the third-line setting. The limitation of this cost-effectiveness analysis, and the reason there is no upper bound on the ICER, is the lack of direct comparative effectiveness data. With a lack of head-to-head trial data, it is difficult to determine the incremental benefits of crizotinib.

## ADOPTION FEASIBILITY

### Considerations for implementation and budget impact: Assumes ROS1 testing will be borne in the treatment-funded scenario

The submitted BIA assumes that the impact of testing will be borne in the treatment-funded scenario; no testing costs are assumed in the reference scenario as no testing is currently taking place for patients with an ROS1 mutation. The submitted BIA results are for Ontario only. In the treatment-funded scenario, it was assumed that nearly all eligible patients would receive crizotinib. The factors that most influence the BIA include the number of eligible patients who are ROS1 positive and the market share.

PAG requested information and clarification on the treatment criteria for crizotinib. PAG requested confirmation that mutations are mutually exclusive and requested guidance on how patients with more than one mutation would be treated. PAG is also seeking guidance on treatment sequencing with chemotherapy, and PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab). PAG also noted that ROS1 testing is not routinely available in all provinces and that there is no formalized testing process or funding in place for ROS1 in jurisdictions. PAG noted that there will be significant costs associated with ROS1 testing, which would be a barrier to implementation.

# 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 Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
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. Kelvin Chan, who was not present for the meeting.
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate.

### Avoidance of conflicts of interest

All members of the 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 pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review crizotinib (Xalkori) for ROS1-positive NSCLC, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one 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 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 pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

### Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

### 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

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

| PAG Implementation Questions | pERC Recommendation |
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| **Eligible Patient Population**<br>• There are several possible mutations in the advanced NSCLC setting (e.g., ROS1, EGFR, and ALK). PAG is seeking confirmation that these mutations are mutually exclusive and guidance on how patients with more than one mutation would be treated (i.e., which mutation would clinicians treat first).<br>• Crizotinib is associated with poor CNS penetration; PAG is seeking guidance on whether patients with ROS1-positive advanced NSCLC who have CNS involvement would be eligible for treatment with crizotinib. | • Driver mutations (ROS1, EGFR, and ALK) are mutually exclusive. That is, the ROS1 mutation is exclusive of other oncogenic drivers and is considered non-overlapping. It is unlikely that patients will present with more than one mutation at the same time.<br>• In the Ox Onc trial, patients with brain metastases were eligible if they were asymptomatic or were neurologically stable for 2 weeks (if treated). In total, 18.1% of patients presented with brain metastases at baseline. pERC noted that patients with stable brain metastases could derive benefit from treatment with crizotinib. |
| **Sequencing and Priority of Treatments**<br>• PAG is seeking guidance on treatment sequencing with chemotherapy, and PD-1, or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab). PAG is seeking confirmation on whether the same treatment algorithm for crizotinib in patients who are ALK positive would apply for patients who are ROS1 positive.<br>• For patients who are ROS1 positive who have received crizotinib in the first-line setting, PAG is seeking guidance on whether second-line treatment with an ALK inhibitor (e.g., ceritinib, alectinib) would be an option. PAG is also seeking clarity on whether ALK inhibitors can be used interchangeably for patients with an ROS1 mutation and preference for an ALK inhibitor. | • pERC noted that there is currently no clinical trial evidence to inform the sequencing of crizotinib and other available treatments for ROS1-positive NSCLC and therefore sequencing is unknown. However, pERC considered the registered clinicians' clinical opinion regarding the sequencing of therapies that suggested that crizotinib would be given as first-line treatment, followed by a next-generation inhibitor (targeted therapy) if a patient progresses after crizotinib. However, pERC noted that there are no other targeted therapies available at this time. Patients who progress on ROS1-targeted therapy would move on to platinum doublet chemotherapy. Immunotherapy with PD-1 or PD-L1 inhibitors would be reserved for later lines of therapy.<br>• pERC noted that drugs that target ALK, such as lorlatinib and ceritinib, have shown efficacy in treating ROS1. However, other effective ALK inhibitors, such as alectinib, do not show the same efficacy treating ROS1. pERC also noted that registered clinicians noted that ROS1 and ALK share similar homology, however, treatments for these targets should not be used interchangeably. |
| **Companion Diagnostic Test/Other**<br>• PAG noted that ROS1 is not routinely available in all provinces. PAG members noted there is no formalized testing process or funding in place for ROS1 in jurisdictions. Health care resources and coordination to conduct the ROS1 testing in the first-line setting will be required. The significant increase in costs for ROS1 testing is a barrier to implementation.<br>• PAG had concerns related to:<br>  ○ the turnaround time for ROS1 testing<br>  ○ whether all NSCLC patients are required to be tested for ROS1<br>  ○ how testing is performed (i.e., through IHC or FISH or other methods); as patients are | • pERC recognized that ROS1 testing is currently not part of standard of care. pERC agreed that ROS1 testing using a validated test authorized by Health Canada or one that is equivalent to that used in the PROFILE 1001 and Ox Onc trials would be reasonable, such as fluorescence in situ hybridization (FISH). The Committee noted that it would be desirable for jurisdictions to have validated and reliable ROS1 testing available to identify both the relevant patient population and to manage the budget impact. Evidence generation from jurisdictions would be of value in regards to actual numbers of eligible patients and the true budget impact.<br>• Registered clinicians noted that testing for the ROS1 mutation currently occurs using FISH, however it is expected that testing will be done by immunohistochemistry in the future. |

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| currently tested for EGFR, PD-L1, and ALK in the first-line setting, and whether there will enough tissue sample to test for ROS1 as the fourth test. | • Additionally, pERC also noted that there may not be enough tissue sample to test for ROS1 in all NSCLC patients if testing becomes part of upfront testing, which pERC considered to be another barrier to implementation. |

ALK = anaplastic lymphoma kinase; CNS = central nervous system; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; PAG = Provincial Advisory Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.