CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Crizotinib (Xalkori) for ROS1- positive Non-Small Cell Lung Cancer

**May 23, 2019**

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# FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Cancer Care Ontario** compared crizotinib to standard of care for first-line treatment of previously untreated patients with ROS1-rearranged (ROS1+) advanced non-small cell lung cancer (NSCLC).

*Table 1. Submitted Economic Model*

| | |
|---|---|
| Funding Request/Patient Population Modelled | *Adults with previously untreated, ROS1+ advanced NSCLC who are eligible for first-line therapy.*<br>*The Health Canada indication for crizotinib is as monotherapy for use in patients with ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC. However, the majority of patients in the studies included had received at least one prior therapy.* |
| Type of Analysis | *CUA & CEA* |
| Intervention | *Crizotinib monotherapy (see* Figure 1 *below).* |
| Comparator | *Standard of care (see* Figure 2 *below):*<br>• *platinum doublet chemotherapy (cisplatin or carboplatin and pemetrexed)* |
| Year of costs | *2018* |
| Time Horizon | *10 years; cycle length 1 month* |
| Discount rate | *1.5% per annum for costs & effects* |
| Perspective | *Government* |
| Cost of Crizotinib | • $0.52 per mg<br>• At a daily dose of 500 mg, the cost per day is $130.00<br>• The cost per 1 month cycle in the economic model is $7,913.75 |
| Cost of carboplatin (used for 80% of chemotherapy costs)<br><br>* *Price Source: PDRP formulary* | • $0.10 per mg<br>• At an assumed dose of $567.20 mg per cycle, the monthly drug cost is $82.21 |
| Cost of cisplatin (used for 20% of chemotherapy costs)<br><br>* *Price Source: PDRP formulary* | • $0.23 per mg<br>• At an assumed dose of 75 mg/m$^2$ per cycle, the monthly drug cost is $45.81. |
| Cost of pemetrexed maintenance<br><br>* *Price Source: PDRP formulary* | • $0.21 per mg<br>• At an assumed dose of 500 mg/m$^2$, for a 21-day cycle, the drug cost is $279.81 (both induction and maintenance) |
| Type of Model | Markov |
| Model Structure | The model was comprised of 5 health states (see Figure 3 below).<br>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. |
| Key Data Sources | Pooled efficacy estimates for crizotinib and chemotherapy from ROS1+ studies. See **Table 2** & **Table 3** for included studies.<br><br>In addition to the data provided from ROS1+ studies, the submitter provided a scenario analysis using untreated ALK+ advanced NSCLC data as a proxy for this reimbursement request. The EGP did not consider this data as the CGP confirmed that the populations are indeed different and that using the ROS1 positive patient population was more appropriate than a proxy population of ALK positive patients. |

*Figure 1. New treatment pathway with crizotinib*

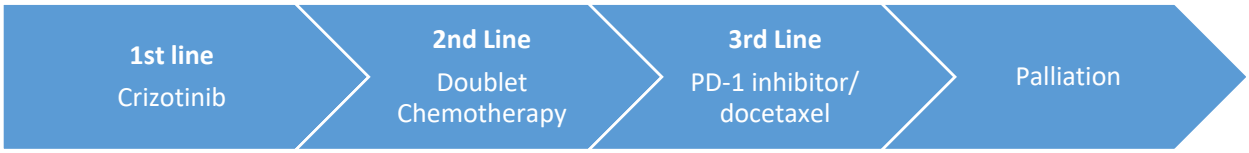
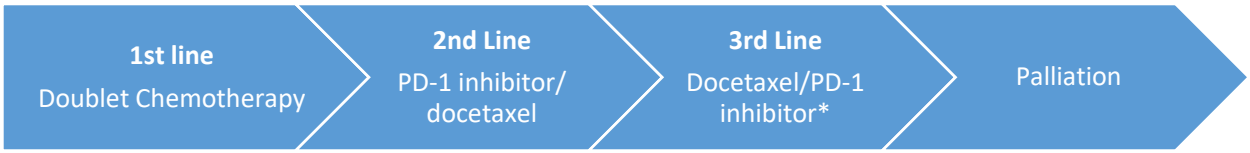



*Figure 2. Standard of care treatment pathway*




*Patients who receive one of a PD-1 inhibitor or docetaxel in second-line may opt to use the other as third-line therapy

*Figure 3. Model structure for Markov model*

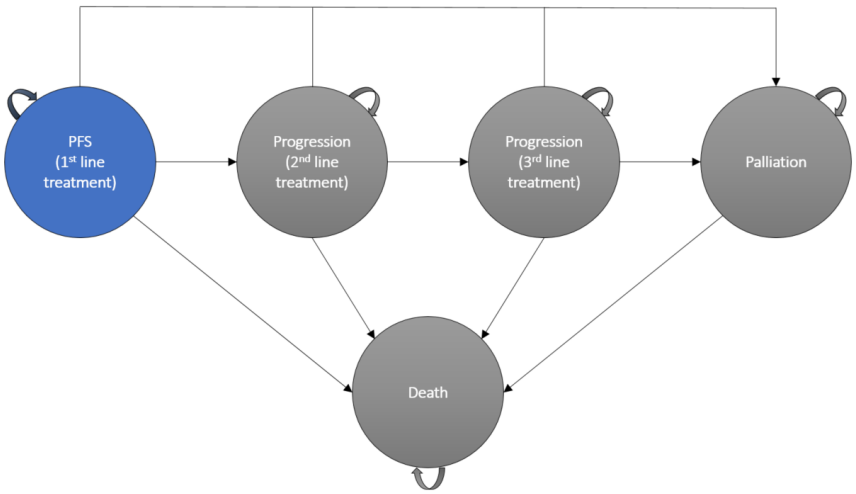


**Table 2: Studies of crizotinib for ROS1+ advanced NSCLC**

| Study | Study Design | Population |
|---|---|---|
| **EUROS1 2015**[1] | Retrospective study(n=31) | • Patients with FISH- confirmed ROS1+ NSCLC<br>• At diagnosis, Stage I-II n=2; Stage III-IV n=29<br>• All patients had stage IV disease at time of crizotinib treatment<br>• Crizotinib as a first- or second-line treatment (n=10, 32%), after two or more lines of chemotherapy (n=21, 68%) |
| **PROFILE 1001**[2] | Open-label, multi-centre single-arm, phase I clinical trial (n=50) | • Eligible patients ≥18 years had histologically confirmed, advanced NSCLC with a ROS1 rearrangement.<br>• ECOG performance status; 0: 22(44%), 1: 27(54%), 2: 1(2%)<br>• Previous regimens for advanced disease 0: 7(14%), 1: 21(42%) and >1: 22 (44%) |
| **Wu 2018**[3] | Single-arm, multicenter phase II clinical trial (n=127) | • Patients had received three or fewer lines of prior systemic therapies for advanced-stage disease or had one or more measurable tumor lesions with and a (ECOG) performance status (PS) of 0 or 1.<br>• Patients enrolled across China, Japan, South Korea, and Taiwan<br>• Other eligibility criteria included three or fewer lines of prior systemic therapies for advanced-stage disease |

**Table 3: Studies of chemotherapy for ROS1+ advanced NSCLC**

| Author | Study Design | Population |
|---|---|---|
| **Drilon 2016**[4] | Retrospective study | • Stage IIIB/IV disease<br>• 7/10 received maintenance pemetrexed |
| **EUROS1 2015**[1] | Retrospective study | • At diagnosis, Stage I-II n=2; Stage III-IV n=29<br>• Stage at treatment NR but pts were stage IV for crizotinib and treatment was described as first or second line for the majority (22, 85%) and later lines in 4 pts |
| **Song 2016**[5] | Retrospective study | • Population from 2 sites in China between Jan 2010 and Dec 2014<br>• At diagnosis: Stage I-IIIA n=19; Stage IIIB-IV n=15<br>• Among the 34 patients, 12 with advanced stage or recurrence were treated with pemetrexed-based first-line chemotherapy.<br>• No maintenance used by any of the 12 patients |
| **Zhang 2016**[6] | Retrospective study | • East Asian population from a single centre in China between Oct 2013 and Feb 2016<br>• ECOG performance status: 0-1: 44 (93.6%) ≥2: 3 (6.4%) |
| **Kim 2013**[7] | Retrospective Study | • Population from Severance Hospital, Seoul, Korea between Jan 2005 and Feb 2012<br>• At diagnosis: Stage I-111A n=3; Stage IIIB-IV n=4 |

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate.

- Relevant issues identified included:
    - There is a net clinical benefit for patients with ROS1 mutations receiving targeted therapy with crizotinib.
    - The level of evidence is limited: there are two published single arm, phase I/II clinical trials of crizotinib with ROS1 positive NSCLC. The overall response rates in these clinical trials were clinically significant, exceeding response rates expected with platinum doublet chemotherapy. There are no randomized trials evaluating crizotinib for ROS1 positive NSCLC patients. The CGP also noted that the sample size of the patient population precludes the feasibility of conducting a randomized controlled trial.
    - Routine testing for ROS1 mutations will be required in order to facilitate treatment decisions with crizotinib. The CGP stated that ROS1 testing is not currently part of standard of care.

**Summary of registered clinician input relevant to the economic analysis**
Registered clinicians input was received from 17 clinicians in a joint input. Clinicians stated that crizotinib was the preferred first-line treatment option for ROS1 mutation patients, with benefits being superior to chemotherapy. Platinum based doublet chemotherapy was stated to be second-line treatment option following ROS1 mutation patients. PD-1 or PD-L1 inhibitors were stated to not show the same efficacy among ROS1 patients, as these patients are predominantly younger and never smokers. Clinicians also found that crizotinib resulted in an improved quality of life. Clinicians also raised that testing for ROS1 is not routine, however, the Canadian ROS initiative aims to render this widely available across Canada. These factors were incorporated into the economic model and reflect the sequencing modeled and the improved efficacy and quality of life with crizotinib.

**Summary of patient input relevant to the economic analysis**
**Patients** with ROS1 mutations are considered to have limited treatment options. Crizotinib provides patients with a treatment that improves progression-free survival and has manageable side effects, compared to the current standard of care of chemotherapy. Crizotinib was also listed to be more convenient in terms of drug administration as it is an oral therapy. Improved survival, increased quality of life and drug administration costs were considered in the economic model.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for crizotinib which are relevant to the economic analysis.

*Enablers*

- The overall number of patients accessing crizotinib who are ROS1 positive is likely to be small.
- The dose of crizotinib is well known as crizotinib is standard of care for first-line ALK positive NSCLC patients.
- Crizotinib is administered orally, chemotherapy units and chair time would not be required.
- Health care professionals are familiar with the administration and monitoring of crizotinib.

*Barriers*

- Oral medications are not funded in the same mechanism as intravenous cancer medications and accessibility may be limited for patients in some jurisdictions.
- Dose reductions of crizotinib may result in a new prescription to be dispensed, which may add to the overall costs of therapy due to drug wastage.
- Additional health care resources may be required to monitor and treat toxicities.
- ROS1 testing is not routinely available in all provinces, and would result in a significant increase in cost.

## 1.3 Submitted and EGP Reanalysis Estimates

*Table 4.* ***Submitted and EGP Reanalysis Estimates***

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 0.885 | 0.577 | N/E |
| 1st line treatment | 0.521 | 0.519 | |
| 2nd line treatment | 0.392 | 0.071 | |
| 3rd line treatment | -0.020 | -0.009 | |
| Palliation | -0.009 | -0.005 | |
| ΔE (QALY) | 0.772 | 0.654 | N/E |
| 1st line treatment | 0.482 | 0.568 | |
| 2nd line treatment | 0.259 | 0.047 | |
| 3rd line treatment | -0.013 | -0.006 | |
| Palliation | 0.044 | 0.045 | |
| ΔC ($) | $210,874 | $205,975 | N/E |
| ICER estimate ($/QALY) | $273,286 | $314,854 | |
| *N/E: Not estimable | | | |

**The main assumptions and limitations with the submitted economic evaluation were:**

- **Lack of comparative effectiveness data:** There is no head-to-head clinical trial of crizotinib versus chemotherapy for the treatment of ROS1+ advanced 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 (Table 2 & Table 3). However, none of the studies included were randomized controlled trials: 2 studies were non-randomized phase 2 and 1 study was retrospective. Some of the data included was collected from retrospective studies, where baseline characteristics of patients may differ. It is difficult to estimate the impact of this on the ICER, as it is unknown what the magnitude of the effect would be in a trial comparing crizotinib to chemotherapy.
- **Comparability of included studies for pooling:** Individual patient data were not available for any of the included studies. It was therefore not possible to adjust for any differences in baseline characteristics and similarities between study populations could only be assessed superficially. Some notable differences included the mix of prior lines of therapy, and results were not stratified according to the number of lines of treatment. It is difficult to estimate the impact of this on the ICER, as individualized patient level data was not available.

- **Median PFS second line (2L) treatment in the crizotinib arm:** For patients in the crizotinib arm, once they progress, they were eligible to received 2L line treatment in the form of platinum-doublet chemotherapy. The median PFS in the second-line in the submitted base case was based on a combined analysis from chemotherapy studies and was calculated to be 7.79 months. The CGP stated that 7.79 months was too long for median PFS in the second line for patients on chemotherapy. A study by Smit et al.[8] identified a median PFS of 4.20 months for these patients. The CGP confirmed that this was more reasonable.
- **Utilities:** None of the identified included ROS1+ studies collected appropriate utility data. The submitter made the assumption that ROS1+ patients were similar to ALK+ patients. In the submitted base case, the utilities from PROFILE 1014[9] were used for crizotinib, however, the submitter felt the values for the chemotherapy arm were too low. Therefore, they calculated a new utility value for the chemotherapy arm based on the value of the crizotinib arm. The CGP stated that there would be a larger difference in utility between the crizotinib and chemotherapy arm for PFS, and therefore the EGP explored the original PROFILE 1014[9] values for each treatment arm in the PFS state.
- **Proportion receiving active therapy in 3rd line:** In the submitted base case, the submitter assumed that of patients in the 2nd line, transitioning to the 3rd line, 60% would receive active treatment. The CGP stated that this proportion was much too high and in reality, only about 30% of patients would receive active treatment, with the remaining patients receiving either palliative care of transitioning to death (50/50 split). The EGP explored this alternate assumption.
- ROS1 testing: The model assumed that testing for ROS1 rearrangement would occur upfront for all patients (and not sequentially after testing negative for other biomarkers). The ROS1 testing was assumed to be conducted using immunohistochemistry (IHC) followed by confirmatory fluorescence in situ hybridization (FISH). The incidence of ROS1 in the base case was assumed to be 1.64%.

## 1.4 Detailed Highlights of the EGP Reanalysis

**The EGP made the following changes to the lower bound in the economic model:**

- Median PFS for 2L treatment in crizotinib arm: The median PFS for 2nd line treatment (patients progression on crizotinib) in the crizotinib arm in the submitted base case was based on a combined analysis of chemotherapy studies. The median PFS was found to be 7.79 months in this combined analysis. The CGP stated that this median PFS was too high for patients who progressed on crizotinib. The submitter provided a scenario analysis of 4.20 months based on a study by Smit et al.[8] The CGP confirmed that this input was more reflective of survival of these patients after progressing on crizotinib.
- Utilities: The submitted base case used values from the PROFILE 1014 study[9] for crizotinib, however, the values for the chemotherapy arm were calculated based on the value for crizotinib. This was done because the submitter felt the reported utility was too low for chemotherapy. The CGP stated that patients on chemotherapy would most likely see a larger drop in utility, as was reported in the PROFILE 1014 study. The EGP used these values in the re-analysis.
- Proportion receiving active therapy in 3rd line: In the submitted base case the submitter assumed that of patients in the 2nd line, transitioning to the 3rd line, 60% would receive active treatment. The CGP stated that this proportion was too high and in reality, approximately 30% of patients would receive active treatment, with the remaining patients receiving either palliative care of transitioning to death.

**The upper bound is not estimable due to the lack of comparative effectiveness data.**

*Table 5.* ***EGP Reanalysis Estimates, probabilistic, 5,000 iterations***

| | ΔC | ΔE QALYs | ΔE LYs | ICUR | Δ from baseline submitted ICER |
|---|---|---|---|---|---|
| Submitted base case | $210,874 | 0.772 | 0.885 | $273,286 | -- |
| **EGP's Reanalysis for the Best Case Estimate** | | | | | |
| **LOWER BOUND** | | | | | |
| *Median PFS for 2L treatment- 4.2 months* | $206,493 | 0.570 | 0.582 | $362,238 | $88,952 |
| *Utilities based on PROFILE 1014 – both treatment arms* | $211,027 | 0.863 | 0.882 | $244,648 | -$28,638 |
| *Proportion receiving active therapy in 3rd line- 30%* | $209,628 | 0.749 | 0.857 | $279,780 | $6,494 |
| **Best estimate of above 3 parameters** | **$205,975** | **0.654** | **0.577** | **$314,854** | **$41,568** |
| **UPPER BOUND** | | | | | |
| *The upper bound is not estimable.* | | | | | |

## 1.5 Evaluation of Submitted Budget Impact Analysis

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 testing for the ROS1 mutation is not currently part of standard of care. For treatments in the current scenario, all patients are assumed to receive first-line doublet chemotherapy with or without pemetrexed maintenance; pemetrexed maintenance is assumed to be given to 50% of patients. In the treatment-funded scenario, it was assumed that nearly all eligible patients would receive crizotinib.

The factors that most influence the budget impact analysis include:

- *Higher incidence of ROS1+ patients:* Increasing the proportion of cases that are ROS1+ from 1.64% to 2.0%, increases the 3-year budget by 20%

- *Higher market share uptake*: Increasing the market share uptake to 100% over the three years (instead of 80% in year 1, 100% in years 2 and 3), increases the 3-year budget impact by nearly 7%.

Note that the BIA results presented in the EGR are for Ontario only. The submitted BIA model can be run for any province. Extrapolating to other provinces based on population sizes would provide an overall estimate for Canada.

## 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for crizotinib when compared to chemotherapy is:**

- Difficult to estimate, given the lack of comparative effectiveness data.
- At a minimum, the ICER would be $314,854/QALY

- The extra cost of crizotinib is at a minimum $205,975 (ΔC). *The main factors that influence ΔC are the source of PFS data (ROS1+ vs ALK+) and the time horizon. Note that the EGP, based on feedback from the CGP, felt that despite the limitations of a pooled analysis, using the ROS1 positive patient population was more appropriate than a proxy population of ALK+ patients.*
- The extra clinical effect of crizotinib is at a minimum 0.654 QALY (ΔE). *The main factors that influence ΔE are the median PFS for 2L treatment in the crizotinib arm and the hazard ratio for PFS pemetrexed maintenance. Note that the CGP felt it was appropriate that patients on pemetrexed maintenance had an increase survival benefit.*

**Overall conclusions of the submitted model:**

- *The model structure was appropriate and addressed the sequencing for this patient population. The model was also well designed.*
- *The single largest limitation of this cost-effectiveness analysis, and the reason there is no upper bound on the ICER, is the lack of comparative effectiveness data. As with other CADTH reviews, with a lack of head-to-head trial data, it is difficult to determine with any certainty the incremental benefits of the new treatment. However, it should be acknowledged that a head-to-head clinical trial with an appropriate comparator in this population is unlikely due to feasibility issues, and the clinicians support a net clinical benefit with the use of crizotinib.*

# 2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

# 3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Crizotinib (Xalkori) for ROS1 positive NSCLC. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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