pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Crizotinib (Xalkori) Resubmission for Advanced or Metastatic Non-Small Cell Lung Cancer

July 3, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of crizotinib (Xalkori) on patient outcomes compared with standard therapies or placebo in previously-untreated patients with anaplastic lymphoma kinase (ALK)-positive advanced or metastatic non-small cell lung cancer (NSCLC).

Crizotinib is an ALK tyrosine kinase inhibitor (TKI) and has a Health Canada indication for use as monotherapy in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label phase III trial, PROFILE 1014, which randomized patients 1:1 to receive crizotinib (n=172) or pemetrexed-plus-platinum chemotherapy (n=171). Patients entered into the trial had ALK-positive, advanced or metastatic NSCLC and had received no previous systemic treatment for advanced NSCLC. Key demographic and baseline characteristics were balanced between the crizotinib and pemetrexed-plus-platinum chemotherapy groups. Patients were stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and race (Asian, non-Asian). The majority of patients in the trial (94% and 95%, respectively in the crizotinib and chemotherapy arms) had an ECOG PS of 0-1. The choice of platinum chemotherapy (carboplatin or cisplatin) was made by the investigator.

Crizotinib was administered orally at 250 mg BID until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Pemetrexed-plus-platinum was administered in 3-week cycles up to a maximum of 6 cycles. Cross over from the chemotherapy to the crizotinib arm was allowed upon disease progression as confirmed by independent radiologic review if safety screening criteria were met and 109 patients (63.7%) in the pemetrexed-plus-platinum chemotherapy group crossed over to the crizotinib group upon disease progression.

Efficacy

The primary outcome was progression-free survival (PFS). At the November 30, 2013 data cut-off, crizotinib had significantly prolonged progression with a median PFS of 10.9 vs. 7.0 months for patients randomized to crizotinib vs. pemetrexed-plus-platinum chemotherapy, respectively (hazard ratio [HR] 0.45 [95% CI: 0.35 to 0.60]).

For key secondary outcomes, median overall survival (OS) was not reached in either group nor was a statistically significantly difference seen between the two arms. Crossover of patients into the crizotinib arm (63.7%) confounded the OS analysis. Adjusting for crossovers suggested a trend in survival benefit with crizotinib over pemetrexed-plus-platinum chemotherapy, but this was not statistically significant. Objective response rate was significantly higher with crizotinib than with chemotherapy (74.4% vs. 45.0%; $p<0.001$).

Crizotinib was associated with a statistically significantly greater improvement from baseline in global quality of life ($p < 0.001$) and in all functioning domains and symptoms (except diarrhea, peripheral neuropathy, constipation, hemoptysis, sore mouth, and

dysphagia) on the EORTC QLQ-C30/QLQ-LC13 scales compared with pemetrexed-plus-platinum chemotherapy.

Harms

Deaths were reported in both arms with 44 and 46 occurring in the crizotinib vs. chemotherapy arms, respectively. Serious adverse events occurred in 33.9% and 27.8% of patients receiving crizotinib and chemotherapy, respectively. Grade 3 to 4 adverse events were similar between the crizotinib and chemotherapy groups, except for elevated transaminases occurring more frequently in the crizotinib arm (14.0% vs. 2.4 while anemia (0% vs 9%) and thrombocytopenia (0% vs 7%) occurred more frequently in the chemotherapy arm.

1.2.2 Additional Evidence

pCODR received input on crizotinib (Xalkori) for advanced NSCLC from two patient advocacy groups, [Lung Cancer Canada (LCC) and Ontario Lung Association (OLA)]. Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

If supplemental questions are addressed as part of the review:

- Summary addressing reliability, cost and feasibility of molecular testing protocol for ALK-rearranged NSCLC in the routine diagnosis of lung cancer

Li et al.[1] conducted a meta-analysis of sixty eight phase 2 and 3 randomized controlled trials of the treatment of advanced NSCLC with the EGFR-TKIs gefitinib and erlotinib showing adequate correlation between progression-free survival and overall survival (R^2=0.74, P<0.001).

A systematic review of meta-analyses evaluating surrogate endpoints for overall survival in oncology trials identified articles evaluating response rate and time to progression as surrogates for overall survival in NSCLC, but not for progression-free survival.[2] However, the review did not include the Li et al.[1] study likely because both were published in the same year (2012). Additional non-systematic reviews[3,4] have likewise indicated a lack of literature and evidence demonstrating progression-free survival as a valid surrogate for overall survival.

Hence, there is limited evidence demonstrating a significant correlation between progression-free survival and overall survival.

1.2.3 Interpretation and Guidance

Non-Small Cell Lung Cancer (NSCLC) remains the leading cause of cancer-related deaths globally with the majority of patients presenting with non-curable disease.[5] It is estimated that in 2015 there will be 26,600 new cases and 20,900 deaths associated with lung cancer in Canada with an incidence and mortality rate of 51.9/100,000 and 40.2/100,000 population, respectively.[6] While the small molecule EGFR tyrosine kinase inhibitors (TKIs); erlotinib, gefitinib and afatinib, now have defined roles in the treatment of patients with EGFR mutant NSCLC; ALK gene rearrangements, more common in adenocarcinomas and light or nonsmokers,[7] are felt to be mutually exclusive of EGFR and KRAS mutations; and occur in approximately 4% of lung cancers, with approximately 400 to 500 ALK positive cases occurring each year in Canada.[8,9]

PROFILE 1014 demonstrated statistically significant improvements in terms of progression-free survival (PFS), symptom control and quality of life (QoL) for crizotinib over standard chemotherapy in patients with ALK-positive advanced or metastatic NSCLC. The safety profile of crizotinib also appears favourable, with the spectrum and incidence of adverse effects in keeping with other oral molecularly targeted anticancer agents used in management of NSCLC.

Therefore, improvement in PFS, symptom control and QoL is sufficient to support use of crizotinib in the first-line setting, particularly as it is associated with modest treatment-related toxicity. Additionally, as a proportion of patients are unable to receive second-line systemic therapy owing to disease progression and performance status, the preference is to use crizotinib, the most effective therapy upfront.

The lack of a clear advantage over standard chemotherapy in terms of overall survival is expected, as it is likely a consequence of crossover.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is a net overall benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC in the first-line setting. This was based on a statistically significant and clinically relevant benefit in terms of PFS, symptom control and QOL compared to standard first-line cytotoxic chemotherapy in one phase III randomized study.

The CGP also considered that from a clinical perspective:

- With establishment of appropriate routine companion ALK mutation testing, the CGP supports use of crizotinib in ALK-positive advanced/metastatic NSCLC patients in the first-line setting.
- As related to treatment sequencing, the preferred option for the ALK-positive NSCLC population is to use crizotinib first-line.
- Crossover is a confounding factor limiting the assessment of crizotinib's impact on overall survival.
- These results are in keeping with other first-line oral targeted agents in molecularly selected patients with NSCLC.

2 CLINICAL GUIDANCE

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

This Clinical Guidance is based on: a systematic review of the literature regarding crizotinib for advanced non-small cell lung cancer conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Crizotinib is an oral anaplastic lymphoma kinase (ALK) selective inhibitor that also has anti-c-Met and ROS activity. Inhibition of phosphorylation of the ALK tyrosine kinase domain down-regulates oncogenic pathways, leading to tumour cell apoptosis among patients with non–small cell lung cancer (NSCLC).[10] Anaplastic lymphoma kinase gene rearrangements – such as the fusion between ALK and echinoderm microtubule-associated protein-like 4 (EML4) – occur in only two to five percent of NSCLC patients, with approximately 400 to 500 ALK positive cases occurring each year in Canada.[8,9]

The manufacturer of crizotinib has a Health Canada approved indication with conditions (NOC/c) for crizotinib (pending the results of studies to verify its clinical benefit) for the monotherapy of patients with ALK-positive advanced (not amenable to curative therapy) or metastatic NSCLC.[11] The recommended dose is 250 mg administered orally twice daily.

A companion diagnostic test, the Vysis ALK break apart fluorescence in situ hybridization (FISH) assay, has been developed to test whether a patient's NSCLC is ALK-positive. Other diagnostic assays – such as IHC, CISH and RT-PCR – are available and are being evaluated for use in identifying ALK-positive NSCLC patients, but they have not been clinically validated in large multicentre studies or evaluated by regulatory agencies. See section 7.1 for more information.

Crizotinib has previously been reviewed by the pCODR Expert Review Committee (pERC) for the treatment of patients with ALK-positive advanced or metastatic NSCLC and received a recommendation to list as a second-line therapy for patients with ALK-positive advanced NSCLC with ECOG performance status ≤ 2, conditional on the cost-effectiveness of crizotinib being improved to an acceptable level.[12]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of crizotinib on patient outcomes compared with standard therapies or placebo in the treatment of previously-untreated patients with anaplastic lymphoma

kinase (ALK)-positive advanced or metastatic non-small cell lung cancer (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One study was included in the systematic review. PROFILE 1014[13] was an open-label, multicentre, randomized, phase III trial of crizotinib versus pemetrexed-plus-platinum (cisplatin or carboplatin) chemotherapy in ALK-positive, advanced or metastatic NSCLC patients who had received no previous systemic treatment for advanced NSCLC. Patients were randomized 1:1 to crizotinib (n=172) or pemetrexed-plus-platinum chemotherapy (n=171), stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and race (Asian, non-Asian). The choice of platinum chemotherapy was made by the investigator. Crizotinib was administered orally at 250 mg BID until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Pemetrexed-plus-platinum therapy was administered at product monograph recommended doses in 3-week cycles up to a maximum of 6 cycles. The primary outcome was progression-free survival according to RECIST v1.1-defined disease progression as determined by independent radiology review, or death. Patients treated with pemetrexed-plus-platinum chemotherapy that had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met. Key secondary outcomes included objective response rate, overall survival, patient-reported outcomes (global quality of life and change in symptoms), and evaluation of safety of crizotinib compared with pemetrexed-plus-platinum chemotherapy.

Key demographic and baseline characteristics were balanced between the crizotinib and pemetrexed-plus-platinum chemotherapy groups in PROFILE 1014.

At the time of the data cut-off date (November 30, 2013), the median duration of treatment was 10.9 months (range 0.4 to 34.3) in the crizotinib group and 4.1 months (range 0.7 to 6.2) in the pemetrexed-plus-platinum chemotherapy group. Crizotinib significantly prolonged progression-free survival (primary endpoint) compared with pemetrexed-plus-platinum chemotherapy: the median progression-free survival was 10.9 months (100 events [58%]) for patients randomized to crizotinib and 7.0 months (137 events [80%]) for patients randomized to pemetrexed-plus-platinum chemotherapy (hazard ratio 0.45 [95% CI: 0.35 to 0.60]). The objective response rate for patients randomized to crizotinib was significantly higher with crizotinib than with chemotherapy (74.4% [95% CI: 67 to 81] vs. 45.0% [95% CI: 37 to 53]; $P < 0.001$).

At the time of the data cut-off date, median overall survival was not reached in either group. At the time of analysis, crizotinib treatment was not associated with statistically significantly longer survival compared with pemetrexed-plus-platinum chemotherapy (hazard ratio [HR] 0.82 [95% confidence interval [CI]: 0.54 to 1.26]). However, 109 (63.7%) patients crossed over from the pemetrexed-plus-platinum chemotherapy arm to the crizotinib arm upon disease progression, which confounded the overall survival analysis. An analysis adjusting for crossover suggested a trend in survival benefit with crizotinib over pemetrexed-plus-platinum chemotherapy, but this was not statistically significant.

Crizotinib was associated with a statistically significantly greater improvement from baseline in global quality of life compared with pemetrexed-plus-platinum chemotherapy ($P < 0.001$). Crizotinib had a significantly greater overall reduction from baseline than chemotherapy in the symptoms of pain, dyspnea, and insomnia as assessed with the use of

the QLQ-C30 and in the symptoms of dyspnea, cough, chest pain, arm or shoulder pain, and pain in other parts of the body as assessed with the use of the QLQ-LC13 (P<0.001 for all comparisons). Crizotinib was also associated with a statistically significantly greater overall improvement from baseline in all functioning domains and symptoms (except diarrhea, peripheral neuropathy, constipation, hemoptysis, sore mouth, and dysphagia) on the EORTC QLQ-C30/QLQ-LC13 scales compared to pemetrexed-plus-platinum chemotherapy. The time to deterioration, defined as the first occurrence of a ≥ 10-point increase from baseline in a composite score of cough, dyspnea, and chest pain from the QLQ-L13, was statistically significantly longer in the crizotinib group compared to the pemetrexed-plus-platinum chemotherapy group (HR 0.62 [95% CI: 0.47 to 0.80]).

In the PROFILE 1014 safety population, 44 deaths occurred among patients receiving crizotinib compared with 46 deaths among patients receiving chemotherapy. Serious adverse events occurred in 33.9% and 27.8% of patients receiving crizotinib and pemetrexed-plus-platinum chemotherapy, respectively. The most common serious adverse events occurring in at least 4% of patients in either arm included disease progression (crizotinib versus chemotherapy, 8.8% vs 0.6%), dyspnea (4.1% vs 2.4%), and pulmonary embolism (2.9% vs 4.1%).

The proportion of patients that experienced an adverse event of any grade was 99.4% in both crizotinib and pemetrexed-plus-platinum chemotherapy groups. Notable differences in reported AE percentages in PROFILE 1014 when comparing crizotinib versus chemotherapy treatment included vision disorder (any grade) (71.3% versus 9.5%), diarrhea (61.4% versus 13.0%), edema (48.5% versus 12.4%), elevated aminotransferases (35.7% versus 13.0%), upper respiratory infection (32.2% versus 12.4%), dysgeusia (26.3% versus 5.3%), anemia (8.8% versus 32.0%), and thrombocytopenia (1.2% versus 18.3%). The severity of most of the AEs in the two treatment groups was low (grade 1 or 2). For example, patients with grade 3 or 4 vision disorder, diarrhea, or edema formed 1%, 2%, and 1%, respectively in the crizotinib group compared to 0, 1%, and 1%, respectively, in the chemotherapy group. Grade 3 to 4 adverse events were similar between the crizotinib and chemotherapy groups, except for elevated transaminases occurring in 14.0% of patients receiving crizotinib compared with 2.4% of patients receiving chemotherapy.

Key limitations of PROFILE 1014 were considered. At the time of the interim analysis, overall survival data was immature and median survival was not reached in either treatment group. The large proportion of patients (%) who crossed over from pemetrexed-plus-platinum chemotherapy to crizotinib makes the overall survival findings difficult to interpret. Although a survival advantage in favour of crizotinib appeared following post hoc statistical adjustment for crossover, the benefit was not statistically significant. Hence, there is a high degree of uncertainty around the overall survival benefit with crizotinib versus pemetrexed-plus-platinum chemotherapy making the findings difficult to interpret. It is also unclear whether the observed statistically significant improvement in progression-free survival and objective response rate with crizotinib versus chemotherapy in PROFILE 1014 correlates with an overall survival benefit. Investigators and patients were not blinded to treatment allocation in PROFILE 1014, but response rates were assessed by Independent Radiology Review which might mitigate potential bias from the lack of investigator blinding; however, patient-reported outcomes are subjective in nature and may have been affected by lack of blinding. The pemetrexed-plus-platinum chemotherapy group only received a maximum of 6 cycles of chemotherapy treatment with no continuation beyond that, while the crizotinib group had no limit on the length of treatment. The effect of this is unclear, however, as studies that have looked at the effect of pemetrexed maintenance therapy only found minor improvements compared to no maintenance therapy.

2.1.4 Comparison with Other Literature

The primary outcome in PROFILE 1014 was progression-free survival. Progression-free survival is often used as a surrogate endpoint for overall survival in phase III oncology trials, and it is accepted by regulatory bodies, such as the U.S. FDA.[14] However, there remains some controversy as to whether improvement in progression-free survival corresponds to prolonged overall survival in advanced NSCLC since, as reported in this systematic review on the evidence from PROFILE 1014 and in previous pCODR reviews, some studies have shown improvement in progression-free survival without a corresponding increase in overall survival.[4]

Li et al.[1] conducted a meta-analysis of phase 2 and 3 randomized controlled trials of the treatment of advanced NSCLC with the EGFR-TKIs gefitinib and erlotinib. Based on sixty-eight trials, multivariate linear models adjusting for patient- and trial-related characteristics showed adequate correlation between progression-free survival and overall survival (R^2=0.74, P<0.001).

A systematic review of meta-analyses evaluating surrogate endpoints for overall survival in oncology trials identified articles evaluating response rate and time to progression as surrogates for overall survival in NSCLC, but not for progression-free survival, thereby indicating a gap in the evidence for progression-free survival as a surrogate endpoint.[2] However, the review did not include the Li et al.[1] study likely because both were published in the same year (2012). Additional non-systematic reviews[3,4] have likewise indicated a lack of literature and evidence demonstrating progression-free survival as a valid surrogate for overall survival.

Hence, there is limited evidence demonstrating a significant correlation between progression-free survival and overall survival. The lack of evidence makes drawing conclusions on the validity of progression-free survival as a surrogate for overall survival in NSCLC difficult.

2.1.5 Summary of Supplemental Questions

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

Summary of ALK Mutation Testing in Advanced or Metastatic Non-small Cell Lung Cancer

The current standard diagnostic test for detecting ALK rearrangement in patients with NSCLC is ALK FISH. The Vysis ALK Break Apart FISH Probe Kit is the only diagnostic assay with regulatory approval in Canada for identifying ALK-positive NSCLC patients who should receive targeted systemic therapy with crizotinib.[15] The Vysis assay was used to identify eligible patients for inclusion into PROFILE 1014.[13] As the current gold standard, the ALK FISH test is capable of detecting any ALK rearrangements including potentially rare, uncharacterized ALK rearrangements. ALK FISH is conducted on FFPE lung cancer tissue with either resection or cytology specimens. One unstained slide cut from the FFPE block is sufficient for ALK FISH testing.[16] However, the conduct of the test and interpretation of the test results require special technical training and equipment that is currently not available in routine laboratory practice throughout Canada and high cost is a consideration. Despite advocacy by the oncology community in Canada in recent years, there is currently no standardized molecular testing protocol for ALK-rearranged NSCLC in the routine diagnosis of lung cancer. Other diagnostic assays – such as IHC, CISH and RT-PCR – are available and are being evaluated for use in identifying ALK-positive NSCLC patients, but they have not been clinically validated in large multicentre studies or evaluated by regulatory agencies. Nonetheless, evidence suggests IHC may be an efficient

and cost-effective alternative to ALK FISH, especially for the initial screening of the larger NSCLC patient population for ALK rearrangements. A two-tiered ALK status screening algorithm has been used in test centres across Canada, in which NSCLC patients would initially be screened with IHC with ALK FISH as confirmatory diagnosis for patients identified as ALK-positive based on IHC.[17-20] A multicentre pan-Canadian study, the CALK project, has reported IHC sensitivity and specificity of 100% and 91.8 %, respectively compared to FISH. It was concluded that the finding supported IHC as a reliable method to screen for ALK-rearranged NSCLC.63 Another CALK study concluded that standardization across multiple centres for ALK testing using IHC and FISH can be achieved. See section 7.1 for more information.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

From a patient perspective, drug therapies for NSCLC that offer an improvement in efficacy, convenience, or side effect profile over the currently available therapies, are important aspects when consideration is given to treatment. Patient input highlighted that patients with ALK positive NSCLC appear to be relatively resistant to EGFR tyrosine kinase inhibitors, such as erlotinib or gefitinib, and tend to have poorer outcomes when treated with chemotherapy and therefore, require alternative treatment options. Patients indicated that crizotinib is the only drug that has demonstrated a benefit in the small subset of patients with ALK positive NSCLC. Patients also noted that crizotinib is associated with minimal side effects, which appear to be manageable for most patients. Patient advocacy groups emphasized the importance of equal funding of crizotinib across all provinces, and also the need to have proper infrastructure in place to test for ALK mutations.

PAG Input

Input on the crizotinib (Xalkori) review was obtained from eight of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that although ALK testing is already available in all provinces, it is only conducted in the second-line setting in some provinces and coordination of health care resources to conduct testing in the first-line setting will be required. PAG noted that information on treatment sequence for patients who progress on crizotinib in the first-line setting would be helpful. PAG noted that there may be a small incremental cost with the shift of using crizotinib in the second-line setting to the first-line setting. PAG also identified that crizotinib is an oral agent which may help to minimize costs related to chemotherapy unit and chair time.

Other

- One ongoing manufacturer-funded trial was identified that is being conducted specifically in East Asian patients. Study A8081029 (NCT01639001 is a phase III, randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed-plus-platinum (cisplatin or carboplatin) in previously untreated East Asian patients with non-squamous NSCLC whose tumours harbor a translocation or inversion event involving the ALK gene locus. The study is expected to enroll at least 200 patients and has an estimated primary completion date of May 2015 (final data collection date for primary outcome measure – progression free survival) and an estimated study completion date of January 2016.

- Crizotinib is administered orally, unlike other available non-targeted treatments for advanced and metastatic ALK-positive NSCLC, which are administered intravenously in outpatient settings. This likely makes crizotinib more convenient for patients to receive.

2.2 Interpretation and Guidance

Non-Small Cell Lung Cancer (NSCLC) remains the leading cause of cancer-related deaths globally with the majority of patients presenting with non-curable disease.[5] It is estimated that in 2015 there will be 26,600 new cases and 20,900 deaths associated with lung cancer in Canada with an incidence and mortality rate of 51.9/100,000 and 40.2/100,000 population, respectively.[6]

The phase III trial comparing crizotinib to standard first-line chemotherapy in patients with ALK-positive advanced or metastatic non-small cell lung cancer (NSCLC) (PROFILE 1014) demonstrates significant efficacy of crizotinib over standard chemotherapy in terms of progression-free survival (PFS) (hazard ratio 0.45 [95% CI: 0.35 to 0.60]), symptom control and quality of life (QOL).

Targeting a driver mutation such as ALK with crizotinib has proven to be a successful treatment strategy. This is supported by the consistent tumour response rates for crizotinib reported between trials in first and subsequent lines of treatment, and various subgroup comparisons, including gender, performance status, ethnicity and smoking status.

The tumour response rates seen with crizotinib in ALK-positive NSCLC patients are significantly greater than what is typically seen with existing standard cytotoxic therapy (74.4% vs. 45.0%). That clinical parameters such as gender, performance status, ethnicity and smoking status do not predict for response to crizotinib highlights the importance of ALK companion laboratory testing to establish ALK positivity for the selection of the appropriate treatment subpopulation.

The safety profile of crizotinib appears favourable, with the spectrum and incidence of adverse effects in keeping with other oral molecularly targeted anticancer agents used in management of NSCLC. Side effects such as ocular toxicity are not expected to have much impact on additional health care services, as they are rare, typically not severe, and reversible with discontinuation of crizotinib. The frequency of adverse effects leading to discontinuation of treatment is low.

Although the ALK-positive population represents a small proportion of all advanced or metastatic NSCLC (in Canada, 3-8%), the annual incidence of NSCLC is large and therefore the absolute number of patients eligible for crizotinib on an annual basis is not inconsequential.

With respect to sequencing of systemic therapies, based on the results of PROFILE 1014 the preferred option for the ALK-positive NSCLC population is to use crizotinib first-line. If ALK positivity is only determined after the initiation of standard first-line chemotherapy, there is the expectation of benefit with crizotinib as salvage therapy. However, a proportion of patients are unable to receive second-line systemic therapy owing to disease progression and performance status. Therefore when ALK-positive status is established at presentation, the preference is to use the most effective therapy upfront (i.e. crizotinib).

Improvement in PFS, symptom control and QOL is sufficient to support use of crizotinib in the first-line setting, particularly as it is associated with modest treatment-related toxicity. The lack of a clear advantage over standard chemotherapy in terms of overall survival is expected, as it is likely a consequence of crossover.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC in the first-line setting. This was based on a statistically significant and clinically relevant benefit in terms of PFS, symptom control and QOL compared to standard first-line cytotoxic chemotherapy in one phase III randomized study.

The Clinical Guidance Panel also considered that from a clinical perspective:

- With establishment of appropriate routine companion ALK mutation testing, the panel supports use of crizotinib in ALK-positive advanced/metastatic NSCLC patients in the first-line setting.
- As related to treatment sequencing, the preferred option for the ALK-positive NSCLC population is to use crizotinib first-line.
- Crossover is a confounding factor limiting the assessment of crizotinib's impact on overall survival.
- These results are in keeping with other first-line oral targeted agents in molecularly selected patients with NSCLC.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Non-Small Cell Lung Cancer (NSCLC) remains the leading cause of cancer-related deaths globally with the majority of patients presenting with non-curable disease.[5] It is estimated that in 2015 there will be 26,600 new cases and 20,900 deaths associated with lung cancer in Canada with an incidence and mortality rate of 51.9/100,000 and 40.2/100,000 population, respectively.[6] The median age at diagnosis for all NSCLC is approximately 70 years of age and unfortunately many of the historical and more recent clinical trials involve advanced stage patients have involved patients significantly younger than the median.[21] Further, the advanced staged population contains a disproportionate number of poor performance patients owing to delayed/late diagnosis and significant co-morbidities, many of which are the result of previous/ongoing tobacco consumption.[22] Crizotinib is an oral ATP-selective inhibitor of ALK tyrosine kinase. ALK gene rearrangements are felt to be mutually exclusive of EGFR and KRAS mutations, and occur in approximately 4% of lung cancers. These mutations are more common in adenocarcinomas and light or nonsmokers.[7]

3.2 Accepted Clinical Practice

Platinum based doublet palliative chemotherapy has been the cornerstone of treatment for patients with advanced stage NSCLC and has resulted in a modest historical increase in overall survival (in the order of an incremental two months increased survival per decade for the past 30 years) and associated quality of life.[2324] The introduction of third generation cytotoxic chemotherapeutic drugs such as vinorelbine, gemcitabine, pemetrexed, paclitaxel and docetaxel paired with platinum agents has resulted in further small improvements,[25-27] although the majority of patients still experience disease progression with a median time to progression of only four months. The small molecule EGFR tyrosine kinase inhibitors (TKIs), erlotinib, and gefitinib and afatinib, now have defined roles in the treatment of patients treatment with EGFR mutant NSCLC. The IPASS study evaluated gefitinib versus carboplatin/paclitaxel in chemotherapy naïve patients. In the EGFR unselected population the study showed no benefit in overall survival, time to progression or response rates (ORR) compared to chemotherapy. However, in patients with EGFR mutated tumours, progression free survival (PFS) was significantly longer (HR 0.48, 95% CI 0.36-0.64, p<0.001).[28] The first phase III study directly comparing erlotinib to standard chemotherapy in the first line advanced setting in patients with an activating EGFR mutation was the OPTIMAL trial that compared erlotinib to gemcitabine/carboplatin resulting in a PFS of 13.1 months with erlotinib versus 4.6 months with chemotherapy (HR 0.16, 95% CI 0.1-0.26, p< 0.001).[29] A second trial (that was the first to involve a western European population), the EUROTAC trial randomized patients to a platinum based doublet regimen (a platinum agent plus docetaxel or /gemcitabine) chemotherapy regimen vs. erlotinib in EGFR mutation unselected patients. In a planned analysis the EGFR mutation positive patients treated with erlotinib had a PFS advantage (9.7 vs. 5.2 months, HR 0.37, 95% CI 0.25-0.54).[30]

3.3 Evidence-Based Considerations for a Funding Population

The role of Echinoderm microtubule associated protein like-4/anaplastic lymphoma kinase (ALK) gene rearrangements and targeted ALK tyrosine kinase inhibitors as active agents in NSCLC patients has been established. ALK gene rearrangements are felt to be mutually exclusive of EGFR and KRAS mutations, and occur in approximately 4% of lung cancers. These mutations are more common in adenocarcinomas and light or nonsmokers.[7] Crizotinib, an oral ATP-selective inhibitor of ALK tyrosine kinase received FDA approval for this indication in 2011. The phase I trial of this agent in advanced, ALK-positive NSCLC revealed a response rate of 57% (95% CI 46-68%) and an estimated 6 month PFS probability of 72% (95% CI 61-83%).[31] A retrospective review of 82 ALK-positive patients (including patients that had received multiple lines of therapy) treated with Crizotinib revealed 1 year survivals of 74% (95% 63-82) and two year survivals of 54% (95% 40-66).[32] Crizotinib was previously reviewed by pCODR as a second-line therapy for patients with ALK-positive advanced non-small cell lung cancer (NSCLC) and the use of crizotinib in previously untreated patients with ALK-positive NSCLC is the topic of this current review. The clinical trial data published and reviewed subsequently in this clinical guidance report only supports this drug's use in advanced NSCLC patients (defined as stage wet IIIB/IV AJCC 6th edition, stage IV AJCC 7th edition) that have tested positive for EML4-ALK fusion protein positive by fluorescent in situ hybridization (FISH) or a combination of ALK immunohistochemistry (IHC) and/or FISH.

3.4 Other Patient Populations in Whom the Drug May Be Used

Crizotinib has potential activity in multiple cancers including those that have driver mutations/amplifications in ALK, c-Met, RON and ROS-1. Cancer histologies that may fall into this group would include sub-populations of NSCLC, non-Hodgkin's lymphoma, neuroblastoma, renal medullary carcinoma, anaplastic thyroid and inflammatory myofibroblastic tumour. To date there is no level 1 (eg. randomized controlled trials) evidence for drug utilization outside of the NSCLC indication and thus should only be considered with the auspices of a clinical trial.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lung Cancer Canada (LCC) and Ontario Lung Association (OLA), provided input on crizotinib (Xalkori) resubmission as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (aNSCLC), and their input is summarized below.

LCC conducted focus groups of patients on crizotinib and their caregivers in February 2015. Five (5) patients and four (4) caregivers participated in the focus group. LCC also conducted one on one interviews with an additional three (3) patients and two (2) caregivers; and one additional patient provided written feedback. In total, LCC received input from nine (9) patients and six (6) caregivers who provided their perspectives into the current submission. Six of the eight patients were under 50 year old and all were under 70 years old. Three of the patients had new infants or school age children. In three cases, the patients were the primary income provider for the family. All nine (9) patient respondents had experience with crizotinib. Of those patients, four (4) patient respondents were receiving crizotinib for first-line treatment.

In addition, LCC also included findings based on supporting materials from Lung Cancer Canada Faces of Lung Cancer Report, which was released in November 2014, as well as literature review.

OLA conducted one phone interview with a patient living with lung cancer, as well as findings from previously completed on-line surveys by both patients and caregivers over the last year. No patients within this evidence group submission have used crizotinib.

From a patient perspective, lung cancer is a devastating illness. According to LCC, lung cancer is the leading cause of cancer death in Canadian men and women, killing more Canadians than breast, prostate and colorectal cancer combined. The 5-year survival rate is approximately 17%. The key symptoms associated with lung cancer includes fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. LCC reported that most Canadians with advanced lung cancer get chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. While response rates are approximately 20%-30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients, both LCC and OLA reported that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. There is also the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC submits that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital. For patients who have not experienced crizotinib, they expect that this drug would stop or slow the progression of the disease, reduce pain, fatigue, cough and shortness of breath, and improve appetite and energy. For patients that have experience with crizotinib, it was reported that crizotinib has minimal side effects, which are manageable for patients, and most importantly dramatically improved outcomes. Common side effects reported included mild nausea and diarrhea. Other common side effects included visual disturbances, mild vomiting, constipation, edema, fatigue, and decreased appetite. LCC indicated that many of these patients are active and high functioning, and living longer than two years on treatment. Additionally, patients are staying out of chemotherapy clinics and hospital, and both they and their caregivers are living more active lives because of this new treatment.

Please see below for a summary of specific input received from the patient advocacy group. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Advanced Non-small Cell Lung Cancer

LCC highlighted that lung cancer is currently the leading cause of cancer-related mortality in Canadians, causing more deaths than breast, ovarian, prostate, and colorectal cancer combined.

According to LCC, advanced stage patients reported that a high proportion of patients experienced lung cancer symptoms: fatigue (100 %), loss of appetite (97 %), shortness of breath (95 %), cough (93 %), pain (92 %), and blood in sputum (63 %). Loss of appetite, cough, pain, and shortness of breath were found to be significant quality of life predictors.

Similarly, OLA reported that the symptoms and problems that patients experience as a result of lung cancer include: pain (very intense at times), shortness of breath, cough, weakness, fatigue, being bed-ridden, and, for some, eventually death. These symptoms are not fixed or consistent, but rather change frequently, which can also be difficult to manage.

Both LCC and OLA noted that lung cancer impacts many aspects of day-to-day life for people living with lung cancer. It affects their ability to work, travel, socialize and participate in leisure and physical activities. It also affects relationships with family and friends, independence, emotional well-being and their financial situation. For some it strips them of their ability to do anything on their own. One respondent stated: "*this disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must use volunteer drivers to get to my appointments, I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful.*"

LCC indicated that lung cancer patients and their families also carry a heavy burden of stigma. As smoking is the leading cause of lung cancer, the stigma associated with this diagnosis is overwhelming. A 2010 national poll showed more than one in five Canadians (22%) said the feel less sympathy for people with lung cancer than those with other cancers because of its link to smoking. Participants of the LCC focus group of patients and their families conducted in October 2014 expressed that they felt the burden of that judgment.

One respondent noted: "*The connection between lung cancer and smoking is very engrained in the public psyche. As a non-smoker with lung caner, I run into a stigma about my disease from time to time. People just don't have exposure to people like me who end up with advanced lung cancer out of the blue*."

4.1.2 Patients' Experiences with Current Therapy for Advanced Non-small Cell Lung Cancer

LCC reported that most Canadians with advanced lung cancer get chemotherapy for first-line treatment of NSCLC, irrespective of their ALK status. Response rates are approximately 20% - 30%, with temporary improvement in symptoms and quality of life in up to two thirds of patients.

LCC indicated that chemotherapy is associated with severe side effects including nausea, vomiting, hair loss, fatigue and the risk of fever and infection. Other side effects may include dehydration, kidney damage, hearing loss and nerve damage. There is also the inconvenience of multiple blood tests, intravenous treatment and multiple visits (with long wait times) to hospital for chemotherapy. LCC submits that this poses a tremendous burden on patients and their caregivers, who must take time off from work to receive treatment, and then additional time off to manage chemotherapy toxicity, including frequent admission to hospital (>10%).

LCC reported that three respondents had either cyber knife treatment or whole brain radiation to treat brain metastases. Respondents noted that compared to crizotinib, this treatment was very debilitating and challenging. One respondent was on bed for 6 months following the treatment and another struggled for 8 months.

According to the respondents, the burden of chemotherapy was felt during all stages of the treatment.

1. Diagnosis: Chemotherapy carried a psychology burden even before receiving the first dose. Those that did not have to go through chemotherapy expressed it as a "relief". "*When I was first diagnosed, the fear of traditional chemotherapy and radiation was overwhelming*". Participants of the focus group used words such as "*cytotoxic killer*" and "*poison*" to describe chemotherapy.

2. Infusion: The Infusions themselves presents challenges beyond travel time and hospital visits. During the infusion, some patients were asked to wear "ice" mittens and socks to in an attempt to minimize the effects of chemotherapy on finger and toe nails. This made the experience of chemotherapy even more challenging and as one respondent described it "painful".

3. Recovery: Significant recovery time was needed after each chemotherapy infusion. For one respondent, this meant "*two bad weeks and one good week. Walking and activity were difficult. I was so sick on infusion chemo. I wasn't functional*". According to LCC, all of those that were on chemotherapy mentioned that chemotherapy took away precious time that they could spend with loved ones due to the side effects. Even when the more acute side effects subsided, their susceptibility to infections due to low white blood counts made spending time with friends and family difficult.

4. Lasting effects of chemotherapy: One respondent that was on chemotherapy felt that you never recover. To this date, 4 years after chemotherapy she still experiences fatigue and has not yet been able to return to work.

OLA reported that the treatments tried by the one respondent interviewed included: glycopyrronium bromide, salmeterol/fluticasone and salbutamol. The respondent is also undergoing radiation and chemotherapy. For respondents who completed the on-line survey, treatments included: tiotropium bromide, salmeterol/fluticasone, budesonide, roflumilast, prednisone, salbutamol, ipratropium bromide, salmeterol, glycopyrronium bromide and indacaterol.

According to OLA, current treatments do provide some relief for fatigue, shortness of breath, cough, appetite loss and low energy, but the side effects such as palpitations, dry mouth, mouth sores, vision and urinary problems and impact on mood need to be better managed. One respondent reported that the radiation has left the respondent with an extremely sore and painful throat. "*I have been burned from my treatments from front to back. I now struggle to swallow, but must eat to re-gain weight and energy. I have also*

lost the feeling in the tips of my fingers and toes. This makes it difficult for me to pick up items, especially money / change when paying for something."

In addition to the above, LCC indicated that the cost of travel is an additional burden, more so in rural communities. Hospital appointments are difficult to obtain and access to chemotherapy suites is limited in both urban areas, and more so in outlying areas.

Similarly, OLA reported that the desire for fewer medical appointments was mentioned several times, as was a wish for less cost burden. For example, due to the weight loss and need for good nutrition, the respondent was instructed to buy certain foods (such as Ensure) and these foods are quite expensive especially for those seniors who are living on a fixed income or on a pension.

LCC also noted that some patients may be deemed unsuitable of chemotherapy, for reasons of performance status, age or other illnesses, further shortening their survival and ability to fight their advanced lung cancer. One respondent in her mid-60's, on chemotherapy and was having a very difficult time; however, her answer sums up the thoughts of many patients and involved three parts: Time to spend with her grandchildren and husband. Hope to beat the disease and, promise of a better treatment (more effective and more tolerable) on the horizon.

4.1.3 Impact of Advanced Non-small Cell Lung Cancer and Current Therapy on Caregivers

LCC received input from three families who cared for a patient receiving crizotinib first line, and one receiving crizotinib second line. Due to brain metastasis, two families had also experienced with whole brain radiation.

Caregivers play an important role in making decisions about treatment and care. During the brief, intense and relentlessly progressive course of advanced lung cancer, caregivers report difficulties in juggling the competing demands of providing emotional and tangible support to patients while meeting the ongoing obligations of home, work, and family. The demands of providing transportation, scheduling and making hospital visits, arranging for home nursing and oxygen support, and managing family finances are physically and emotionally devastating for both cancer patients and their caregivers. Persistent psychological distress and role adjustment problems experienced by caregivers have been reported up to a year after patients have completed treatment for cancer, with levels of distress far higher than those found in healthy controls.

In addition, the physical and emotional demands of care giving reach their peak as lung cancer progresses. Many caregivers and all lung cancer patients must take time off – most people affected by lung cancer are of lower socioeconomic status, and many families are devastated by the loss of one or both earners to lung cancer as patient and caregiver. Intensive chemotherapy requires caregivers both to attend hospital and treatment sessions, as well as to support patients at home through nausea and vomiting, fever and other toxicities.

OLA reported that caregivers of those living with lung cancer experience many of the same negative impacts on their lives as the patients themselves. They too indicate that caring for them has affected their work, finances, relationships with family and friends, and their physical and leisure activities. As well, their independence and the ability to travel and socialize were impacted. An overarching theme was the emotional toll of watching those

with lung cancer suffer in pain, knowing there is little you can do to alleviate the discomfort and pain.

To help illustrate the experiences of caregivers, below are some of the key responses reported by LCC:

1. High management burden of lung cancer – all caregivers felt a high physical burden prior to treatment and while they were on other treatments. This was reflected in all aspects, from the hospital visits to the support of patients at home. "*When [redacted] was not feeling well, all of a sudden, I went from having three children to four children*". Chemotherapy often left caregivers feeling helpless as the side effects carried a high level of unpredictability. Everyone spoke to the challenge of constantly "trying this, or that" to make the patient more comfortable. One respondent stated: "*I was running a short order kitchen*". "*Constantly we would be trying something and then she would have one bite and throw up*". Another respondent stated: "*Crizotinib has allowed me to have a spouse and not a patient. It's allowed me someone I can spend time with instead of taking care off. We went back to the normal dynamic of a mother, a father and three children*". "[redacted] *had a happy simple life on crizotinib – much better – and I had a happy simple life on crizotinib*".

2. Psychological burden of maintaining positivity – All the caregivers felt the need to maintain positivity - to try to stay positive so that their loved ones would not lose hope. One respondent, whose mother is living with lung cancer felt that burden as his mother became depressed after diagnosis. "*She didn't want to live*." Chemotherapy and other treatments made that burden even harder due to the harsh side effects. One respondent stated: "*Being the caregiver it's hard to be positive around someone that is feeling so horribly*". "*You can't be happy and it's impossible to make them happy*."

Time – This concept was very important. The length of time their loved ones were on crizotinib varied, from a low of 4 months to about a year. One respondent continues to be on crizotinib at the time of the call with a duration of 4 years. Another respondent participated in the original 2011 submission is still doing well on crizotinib. She and her husband provided their thoughts in the one-on-one interview as they were spending time together on a road trip. Caregivers felt that crizotinib gave them time with loved ones to do "normal" things. "*Living with lung cancer takes away all normal, but crizotinib gave us a new normal*." They all expressed that it gave them much valued time as a family, to travel to visit with friends. All expressed the idea of a "good" time, even if it was short.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Crizotinib (Xalkori)

OLA noted that key treatment outcomes of lung cancer that patients and their caregivers would most like addressed are to:

- stop or slow the progression of the disease,
- reduce pain, fatigue, cough and shortness of breath, and
- improve appetite and energy.

According to OLA, patients and caregivers would like the following current side effects reduced or eliminated: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. They would also like there to be less or no cost burden associated with new treatments.

OLA also indicated that on a practical level, patients would like the ability to do treatments at home, so it would remove the need for the patient or the caregiver to take time off of work. This would also lead to less disruption of the daily routine.

LCC reported that crizotinib represents a major advance for lung cancer patients. It is an effective, highly active and valuable oral treatment option for patients. Specifically, LCC believes that the evidence for crizotinib versus chemotherapy is vastly superior in terms of outcomes, response rates, symptom improvement, progression free survival and overall survival in ALK-positive aNSCLC patients. The respondents that participated in this submission have a high desire for treatment and are very aware of upcoming new treatments and trials. As ALK+ NSCLC patients tend to be younger and are not smokers, two of the respondents experienced delays in diagnosis as they did not fit the stereotypical older smoker profile. They and their caregivers strenuously pursued medical treatment. When on treatment, they often prepared for when each treatment failed. One respondent stated: "*Crizotinib gave me the time to focus on investigating other treatments for my wife*".

While OLA had no respondents who have used crizotinib, LCC reported that they received a total of nine (9) respondents who have experienced with crizotinib. Of those patients, four (4) patient respondents were receiving crizotinib for first-line treatment.

LCC indicated that many of these patients are active and high functioning, and living longer than 2 years on treatment. This is a revolutionary outcome in this small population of patients with an otherwise extremely grim prognosis. Patients are staying out of chemotherapy clinics and hospital, and both they and their caregivers are living more active lives because of this new treatment.

Respondents reported mild nausea and diarrhea were the most commonly reported side effects, seen in more than one quarter of patients. Other common side effects included visual disturbances (41%), mild vomiting, constipation, edema, fatigue, and decreased appetite. For some, increases in levels of hepatic transaminases were generally mild, and even if more severe, are usually without symptoms. According to LCC, side effects were manageable for patients, and most importantly dramatically improves outcomes.

Below are key findings and comments that were reported by LCC based on patients' experience with crizotinib.

1) *Crizotinib gave me confidence*!
This confidence came from two aspects. LCC reported that crizotinib helped achieve dramatic tumour shrinkages in the vast majority of respondents that were interviewed. It also had a dramatic effect on the symptoms of lung cancer – cough, shortness of breath, fatigue, pain. The effect was rapid with patients saying that they are feeling better within a few days to a month.

One respondent stated: "*My wife took crizotinib on Friday and on Sunday she was able to get out of bed and we went outside for a walk*".

Psychologically, this really helped all the patients feel better and believe in treatment, and the possibility of a future. One respondent noted that his mother went from being depressed to really believing that things would be ok. She was feeling better and able to fully participate in her daughter's wedding. Another respondent said, getting rid of the cough was a "*morale" victory*!"

2) *Crizotinib made things "normal"*
One respondent reported: "*Crizotinib took me from being a sick always sick cancer patient, to being almost able to live a normal life I was able to work and start to work out, be a mom. Everything dramatically changed*".

According to LCC, some respondents had symptoms of lung cancer (pain, shortness of breath, fatigue, cough etc.). Others did not have any symptoms at all, or very mild symptoms. Respondents that participated in this submission felt that crizotinib helped to enable normalcy, and as for those that had symptoms, it was felt to work quickly. For those that had little or no symptoms, it enabled them to continue life as they have known it with little disruption. As one respondent said, "*It established a new good normal*."

This normal included allowing this to do meaningful things in life; for example, returning to life, to continue to work, to parent their children. As one respondent stated, "*Crizotinib has made things very normal. My colleagues see me at work almost every day*." Another respondent was able to continue to be true parent and not a patient. Another respondent reported that six years after being diagnosed and after being on crizotinib for four years, the respondent is looking forward to getting married this spring.

3) *Crizotinib had manageable side effects*
Respondents felt that side effects were manageable. The most commonly reported side effects were nausea, diarrhea and vision disturbances. One respondent experienced more severe diarrhea than the others but stated: "*In six weeks, my tumour was half the size it was and in 12 weeks it was quarter of the size. I was symptom free and off oxygen. I was back to being myself. I looked so good that I was apologizing for looking so good!*"

Respondents, however, did want to remind other patients who are on crizotinib should have regular brain scans. Brain metastasis are common in lung cancer patients and it was felt that crizotinib had limited ability to cross the blood brain barrier.

4) *Crizotinib made hope easier!*
One respondent reported: "*On crizotinib, the hope I was trying to portray was right in front of me*." She went from "*crying every night in the shower so my boys would not hear me,*" to ""*It's going to ok*""

Another respondent stated: "*It was difference between viewing your life as a 2–5 year termination point to having a future and not a death sentence, and really believing that you could live as long a life you always imagined*."

A third respondent stated: "*Thinking back to when I was diagnosed, I never thought that I would live five years. Having crizotinib as an option filled me with hope. I went from thinking of my life would end shortly to managing it as a chronic illness*".

4.3 Additional Information

LCC highlighted that there would only be a small population of patients eligible to receive crizotinib therapy, as only 2-7% of patients with advanced NSCLC have ALK positive disease.

Gene targeted therapy has changed the paradigm for the treatment of lung cancer and have started the path towards truly personalized medicine. EGFR TKI's, treatments

targeting EGFR mutations, have been adopted in Canada as first line treatment for EGFR positive NSCLC patients. The National Comprehensive Cancer Network (NCCN) in the US guidelines recommends the use of crizotinib first line in ALK+ patients. As such, LCC submits that Canadian ALK+ patients should receive the same standard of care and access to the same medications as other ALK+ patients in other parts of the world.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from the eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could be impact implementation of crizotinib in the first-line treatment of ALK positive non-small cell lung cancer (NSCLC):

Clinical factors:

- Small sub-group of patients with ALK positive NSCLC
- Treatment sequence after progression on crizotinib first-line

Economic factors:

- Small incremental budget increase in shifting crizotinib to first-line setting

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that the standard first-line therapy for patients with EGFR mutation-positive NSCLC would be gefitinib or afatinib. Cisplatin plus pemetrexed is the standard first-line treatment for patients who are not EGFR mutation-positive and are ALK positive.

Although NSCLC is a common cancer, PAG noted that crizotinib would only be indicated for patients who were ALK positive. As there would only be a small subset of patients who were ALK positive, the overall numbers of patients accessing crizotinib is likely to be small. This is an enabler to implementation.

Crizotinib is already funded in the second-line treatment of ALK positive NSCLC and would be an oral treatment option in the first-line setting for ALK positive NSCLC. PAG members report already receiving funding requests for use of crizotinib in the first-line treatment.

PAG is seeking whether information is available on treatment sequence for these patients when progression occurs on crizotinib in the first-line setting.

5.3 Factors Related to Dosing

PAG noted that dosage reductions of crizotinib (250mg BID, then 200mg BID, then 250mg QD if further reductions are required) may be required in situations where the patient is experiencing tolerability or side effect issues. Some jurisdictions noted that the decrease to 200mg BID would require a new prescription to be dispensed, which may add to the overall costs of therapy due to drug wastage. This also causes potential risk for medication errors.

5.4 Factors Related to Implementation Costs

As crizotinib is administered orally, PAG identified that chemotherapy units and chair time would not be required. In addition, health care professionals are familiar with the administration and monitoring of crizotinib. These are enablers to implementation.

PAG noted that there may be a small incremental cost with the shift of using crizotinib in the second-line setting to the first-line setting.

PAG also noted that additional health care resources may be required to monitor and treat toxicities, in particular, ophthalmologists to monitor for ocular toxicities.

5.5 Factors Related to Health System

PAG noted that ALK testing is already available in all provinces. However, in some provinces, the ALK testing is conducted in the second-line setting and coordination of health care resources to conduct the ALK testing in the first-line setting will be required. PAG also noted that there are delays to initiation of treatment due to the delay in ALK testing results and in some cases, the ALK testing results are not available until after patients have commenced treatment.

PAG noted that crizotinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.6 Factors Related to Manufacturer

PAG identified that the flat pricing of the two strengths of tablets is a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of crizotinib on patient outcomes compared with standard therapies or placebo in the treatment of previously-untreated patients with anaplastic lymphoma kinase (ALK)-positive advanced or metastatic non-small cell lung cancer (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Summary addressing reliability, cost and feasibility of a molecular testing protocol for ALK-rearranged NSCLC in the routine diagnosis of lung cancer

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention*	Appropriate Comparators*†	Outcomes
Published or unpublished RCTs or controlled clinical trials	Previously untreated patients with ALK-positive advanced or metastatic NSCLC <u>Subgroups:</u> • Prior adjuvant chemotherapy • Histologic type • ECOG PS (0—1 vs. ≥2) • Sex • Race • Smoking status • EGFR mutation status	Crizotinib as monotherapy at recommended dose 250 mg orally twice daily	**Active** Cytotoxic Chemotherapies (with Platinum Doublet agent): • Pemetrexed • Docetaxel • Paclitaxel • Gemcitabine • Vinorelbine₴ **Non-active** • Placebo	• Overall survival • Progression-free survival • **QOL** • Objective response rate • **SAEs** • **AEs** • WDAEs

AE=adverse events; **ALK**=anaplastic lymphoma kinase; **CR**=complete response; **ECOG PS**=Eastern Cooperative Oncology Group Performance Status Scale; **EGFR**=epidermal growth factor receptor; **QOL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events

Note: *the highlighted section under the Clinical Trial Design criteria was the only change made to the original systematic review protocol for the crizotinib resubmission.*

** All treatments in combination with supportive care.*

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

₴ alone or paired with a platinum-doublet agent

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Xalkori and crizotinib.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of June 4, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

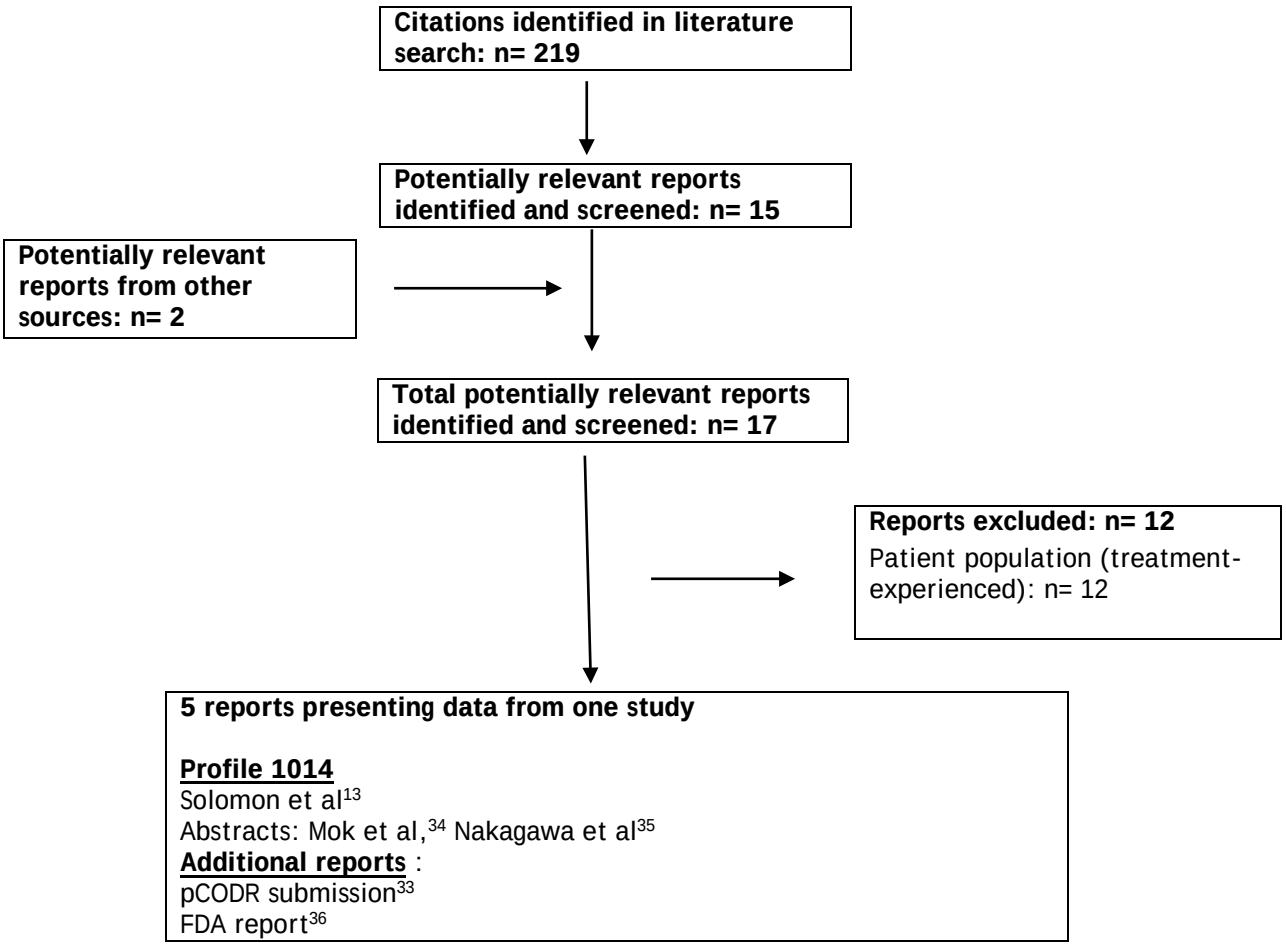
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 17 potentially relevant reports identified, 5 reports were included in the pCODR systematic review[13,33-36] and 12 studies were excluded. Studies were excluded because they were conducted in the wrong patient population (treatment-experienced).[37-48]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the PROFILE 1014 study was also obtained through requests to the Submitter by pCODR[49]

6.3.2 Summary of Included Studies

Crizotinib has previously been reviewed by the pCODR Expert Review Committee (pERC) for the treatment of patients with ALK-positive advanced or metastatic NSCLC and received a recommendation to list as a second-line therapy for patients with ALK-positive advanced NSCLC with ECOG performance status ≤ 2, conditional on the cost-effectiveness of crizotinib being improved to an acceptable level.[12] This systematic review focuses on crizotinib for the treatment of patients with ALK-positive advanced NSCLC who had received no previous treatment for advanced NSCLC.

One clinical trial met the inclusion criteria for this systematic review. PROFILE1014 was a multicenter, phase III, randomized, open-label study that evaluated the efficacy and safety of crizotinib compared to pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced (locally advanced or metastatic) ALK-positive NSCLC.[13,34-36] A summary of PROFILE1014 is presented in Table 2.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included Study[13,33-36]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
PROFILE1014 (Study A8081014) January 13, 2011 – July 2013 (dates of enrollment and randomization) Data cutoff: November 30, 2013 Phase III, multicenter, multinational, OL RCT n = 334 planned n = 343 enrolled n = 340 treated Funded by: Pfizer (manufacturer)	• ≥ 18 years • Histologically or cytologically confirmed locally advanced/metastatic NSCLC • ALK mutation (translocation nor inversion determined by ALK break-apart FISH assay) • Received no previous systemic treatment for advanced NSCLC • ECOG-PS ≤ 2 • Measurable disease • Treated brain metastases allowed • Adequate organ function *Stratification factors* • ECOG-PS (0/1 vs. 2) • Brain metastases (present/absent) • Race (Asian/non-Asian)	*Intervention* Crizotinib 250 mg orally BID (n = 171; n = 1 randomized did not receive crizotinib) *Comparator* Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 Or Carboplatin target AUC 5 to 6 mg/mL/min 21-day cycles (maximum 6 cycles) (n = 169; n = 2 randomized did not receive chemotherapy)	*Primary* • Progression-free survival (RECIST v.1.1) *Secondary* • Objective response rate (RECIST v. 1.1) • Overall survival • Adverse events • Patient-reported outcomes (QLQ-C30, QLQ-LC13, EQ-5D)

AUC = area under the curve; **BID** = twice daily; CR = complete response; **DB** = double-blind; **ECOG-PS** = Eastern Cooperative Oncology Group performance status; **EQ-5D =** EuroQol Group 5-Dimention Self-Report Questionnaire; **FISH** = fluorescent in-situ hybridization; **NSCLC** = non-small cell lung cancer; **OL =** open label; **PR** = partial response; **QLQ-C30 =** quality of life core questionnaire; **QLQ-LC13 =** quality of life questionnaire lung cancer module; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT** = randomized controlled trial

a) Trials

PROFILE 1014 was a phase III randomized controlled trial of crizotinib (n=172) versus pemetrexed-plus-platinum chemotherapy (n=171), in ALK-positive, advanced and metastatic NSCLC patients who had received no previous systemic treatment for advanced NSCLC. Patients also had to have an ECOG performance status of ≤ 2. Patients with treated brain metastases were eligible for inclusion if the metastases were neurologically stable for at least two weeks before enrollment and if the patient had no ongoing requirement for glucocorticoids.

Patients were randomized 1:1 to crizotinib or pemetrexed-plus-platinum chemotherapy, stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and race (Asian, non-Asian). Randomization was performed using a centralized permuted block design using an Interactive Voice Response System or website.[49] The choice of platinum chemotherapy was made by the investigator.

The primary outcome of PROFILE 1014 was progression-free survival. Patients continued on treatment until RECIST (v1.1)-defined progressive disease as assessed by independent radiologic review, or death. Patients treated with pemetrexed-plus-platinum chemotherapy who had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met. Key secondary outcomes included objective response rate, overall survival, patient-reported outcomes (global quality of life and change in symptoms), and evaluation of safety of crizotinib compared with pemetrexed-plus-platinum chemotherapy.

The final analysis of progression-free survival was specified to be conducted after 229 events of disease progression or death due to any cause were observed; interim analysis was planned at 45% to assess safety and futility for PROFILE 1014.[71] There was no pre-specified number of deaths reported at which the final overall survival analysis would be conducted. The sample sizes were based on detecting a 50% improvement in progression-free survival with crizotinib versus pemetrexed-plus-platinum chemotherapy with 85% power (one-sided $\alpha = 0.025$) and that a 50% improvement in the median PFS (to 9 months) in Arm A is clinically meaningful.[71] A step-down procedure was applied to the efficacy endpoints to control for Type I error for the comparison between crizotinib and pemetrexed-plus-platinum chemotherapy in the following order: progression-free survival, objective response rate, and overall survival.

The Kaplan-Meier method was used to estimate time-to-event endpoints. Two-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of progression-free survival and overall survival; stratified Cox regression models were applied to estimate hazard ratios. Overall survival was also analyzed with the rank-preserving structural failure time model to explore the effect of crossover to crizotinib in the pemetrexed-plus-platinum chemotherapy group. All analyses in the pemetrexed-plus-platinum chemotherapy group except for overall survival included only data collected before crossover to crizotinib. A two-sided stratified Cochran-Mantel-Haenszel test was used to compare the objective response rate between treatment groups. Safety evaluations were performed in the as-treated population and safety results were not adjusted for the shorter duration of treatment in the chemotherapy group. Patient-reported outcomes were evaluated in patients in the intention-to-treat population who also had a baseline assessment and at least one post-baseline assessment. Patient-reported outcomes were assessed at baseline, on days 7 and 15 of cycle 1, on day 1 of every subsequent cycle, and at the end of treatment. Repeated-measures mixed-effects modeling was performed to compare the two treatment groups with respect to the overall change from baseline scores on the quality of life scales using two-sided tests that were not adjusted for multiple testing.

Subgroup analyses were pre-specified except for the analyses by chemotherapy type. For progression-free survival, 20 subgroup analyses were performed with a probability of false-positive findings of 64%. For objective response rate, 10 subgroup analyses were performed (probability of false-positive findings, 40%). For overall survival, 25 subgroup analyses were performed (probability of false-positive findings, 72%).

b) Populations

Key demographic and baseline characteristics for patients in PROFILE 1014 were balanced between the crizotinib and pemetrexed-plus-platinum chemotherapy groups as shown in Table 3. The median age was 52 to 54 years and over 60% of the patients were female. The majority of patients had an ECOG performance status of 0 or 1, were non-smokers or former smokers, had metastatic disease, had a histologic subtype of adenocarcinoma, and had no brain metastases.

Table 3: Baseline Patient Characteristics for PROFILE 1014[13]		
	Crizotinib (n = 172)	**Chemotherapy (n = 171)**
Male, n (%) Female, n (%)	68 (39.5) 104 (60.5)	63 (36.8) 108 (63.2)
Age, median years [range]	52 [22 to 76]	54 [19 to 78]
Race, n (%) White Asian Other	 91 (52.9) 77 (44.8) 4 (2.3)	 85 (49.7) 80 (46.8) 6 (3.5)
ECOG performance status, n (%) 0 or 1 2	 161 (93.6) 10 (5.8)	 163 (95.3) 8 (4.7)
Smoking status, n (%) Never smoked Former smoker Current smoker	 106 (61.6) 56 (32.6) 10 (5.8)	 112 (65.5) 54 (31.6) 5 (2.9)
Stages, n (%) Locally advanced Metastatic	 4 (2.3) 168 (97.7)	 3 (1.8) 168 (98.2)
Histologic subtype, n (%)[69] Adenocarcinoma Large cell carcinoma Adenosquamous carcinoma Other	 158 (91.9) 3 (1.7) 5 (2.9) 6 (3.5)	 159 (93.0) 8 (4.7) 1 (0.6) 3 (1.8)
Brain metastases, n (%) Present Absent	 45 (26.2) 127 (73.8)	 47 (27.5) 124 (72.5)
Global quality of life score (QLQ-C30), mean ± standard deviation	61.2 ± 24.9	59.4 ± 24.8
General health status (EQ-5D), mean ± standard deviation	70.8 ± 19.7	66.6 ± 21.9
ECOG = Eastern Cooperative Oncology Group		

c) Interventions

Patients were randomized to receive oral crizotinib at a dose of 250 mg BID, or intravenous pemetrexed 500 mg/m^2 on Day 1 of every cycle plus either cisplatin 75 mg/m^2 or carboplatin target area under the curve of 5 to 6 mg/mL/min. The choice of platinum therapy was made by the investigator. Crizotinib was administered until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Continuation of crizotinib beyond disease progression was allowed for patients who had been randomly assigned to crizotinib if the patient was perceived by the investigator to be having clinical benefit. Pemetrexed-plus-platinum therapy was administered in 3-week cycles up to a maximum of 6 cycles. If a patient completed the 6 cycles of chemotherapy, the patient was to remain in the study with no additional treatment until RECIST-defined progressive disease. Patients that had RECIST-defined progressive disease as determined by independent radiologic review in the pemetrexed-plus-platinum group were allowed to crossover to receive crizotinib treatment.

d) Patient Disposition

The data cutoff date for PROFILE 1014 was November 30, 2013. A total of 79 patients (45.9%) in the crizotinib group and 62 patients (36.3%) in the pemetrexed-plus-platinum chemotherapy group were on treatment at the time of data cutoff; the patients in the chemotherapy group were continuing treatment with crizotinib after crossover. A total of 108 patients (63.2%) completed

the maximum 6 cycles of pemetrexed-plus-platinum chemotherapy. The most common reason for treatment discontinuation was disease progression in both groups (Table 4). One hundred and nine patients (63.7%) in the pemetrexed-plus-platinum chemotherapy group crossed over to the crizotinib group upon disease progression. One patient who crossed over had their disease progression confirmed by the investigator and not by independent radiologic review.

Table 4: Patient Disposition for PROFILE 1014[13]

	Crizotinib	Chemotherapy
Randomized, n (%)	172 (100)	171 (100)
Received allocated treatment, n (%)	171 (99.4)	169 (98.8)
Pemetrexed + Cisplatin, n (%)	Not applicable	91 (53.2)
Pemetrexed + Carboplatin, n (%)	Not applicable	78 (45.6)
Safety population, n (%)	171 (99.4)	169 (98.8)
Completed chemotherapy cycles, n (%)	Not applicable	108 (63.2)
Still on treatment, n (%)	79 (45.9)	62 (36.3)[†]
Discontinued, n (%)	92 (53.5)	61 (35.7)
Adverse events	12 (7.0)	16 (9.4)
Progressive disease*	52 (30.2)	25 (14.6)
Death	6 (3.5)	4 (2.3)
Global deterioration of health status	12 (7.0)	6 (3.5)
Lost to follow-up/Patient decision	9 (5.2)	5 (2.9)
Other	1 (0.6)	5 (2.9)
Crossover to crizotinib	Not applicable	109 (63.7)

[†]patients continuing on treatment in crossover
*Objective progression or relapse

e) Limitations/Sources of Bias

- The large percentage of patients who crossed over from pemetrexed-plus-platinum chemotherapy to crizotinib makes the overall survival findings in PROFILE 1014 difficult to interpret. There were differential crossover patterns between the two treatment groups, where most pemetrexed-plus-platinum chemotherapy patients crossed over to crizotinib and continued treatment, often longer than the original chemotherapy treatment. Although a survival advantage in favour of crizotinib appeared following post hoc statistical adjustment for crossover, the benefit was not statistically significant. Hence, there is a high degree of uncertainty around the overall survival benefit with crizotinib versus pemetrexed-plus-platinum chemotherapy making the findings difficult to interpret.
- In addition, there was no pre-specified number of events reported in the publication at which the final overall survival analysis would be performed;
- It is unclear whether the observed statistically significant improvement in progression-free survival and objective response rate with crizotinib versus chemotherapy in PROFILE 1014 correlates with an overall survival benefit.
- Subgroup analyses, despite being pre-specified, would inflate Type I error.
- Patient-reported outcomes were not included in the step-down procedure and may therefore be subjected to Type I error; in addition, the analyses for patient-reported outcomes did not use a true intention-to-treat population as patients needed to have a baseline score to be included.
- No blinding of investigators or patients in PROFILE 1014; response rates were assessed by Independent Radiology Review which might mitigate potential bias from the lack of

investigator blinding; however, patient-reported outcomes are subjective in nature and may have been affected by lack of blinding.

- The pemetrexed-plus-platinum chemotherapy group only received a maximum of 6 cycles of chemotherapy treatment with no continuation beyond that, while the crizotinib group had no limit on the length of treatment. The effect of this is unclear, however, as studies that have looked at the effect of pemetrexed maintenance therapy only found minor improvements compared to no maintenance therapy. In addition, it would be difficult for patients to tolerate more than 6 cycles of chemotherapy treatment.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Results are presented according to the hierarchy of outcomes established in the systematic review protocol (section 6.2.1). As of the study cutoff dates, the median duration of treatment was 10.9 months (range 0.4 to 34.3) in the crizotinib group (median 16 cycles [range 1 to 50]) and 4.1 months (range 0.7 to 6.2) in the pemetrexed-plus-platinum chemotherapy group (median 6 cycles [range 1 to 6]). The median duration of follow-up for overall survival was 17.4 months patients assigned to crizotinib and 16.7 months for patients assigned to pemetrexed-plus-platinum chemotherapy.

Table 5: Summary of Key Outcomes[13]

Efficacy	**Crizotinib (n = 172)**	**Chemotherapy (n = 171)**
Overall survival, median [95% CI] months HR [95% CI] 2-sided p-value (stratified log rank)	NR 0.82 [0.54 to 1.26] 0.361	NR
Progression-free survival, median [95% CI] months HR [95% CI] 2-sided p-value (stratified log rank)	10.9 [8.3 to 13.9] 0.45 [0.35 to 0.60] < 0.001	7.0 [6.8 to 8.2]
Objective response rate, n (%) [95% CI] 2-sided p-value (stratified CMH) Complete response Partial response	128 (74.4) [67 to 81] <0.001 3 (1.7) 125 (72.7)	77 (45.0) [37 to 53] 2 (1.2) 75 (43.9)
Time to response, median [range] months	1.4 [0.6 to 9.5]	2.8 [1.2 to 8.5]
Harms, n (%)	**Crizotinib (n = 171)**	**Chemotherapy (n = 169)**
Deaths	44 (25.6)	46 (26.9)
SAEs	58 (33.9)	47 (27.8)
AEs	170 (99.4)	168 (99.4)
WDAEs	21 (12.3)	24 (14.2)

AE= adverse event; **CI** = confidence interval;CMH = Cochran-Mantel-Haenszel; **NR** = not reached; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event

Efficacy Outcomes

Overall survival

Overall survival was a secondary outcome in PROFILE 1014. At the time of the data cut-off, the median duration of treatment was 10.9 months (range 0.4 to 34.3) in the crizotinib group and 4.1 months (range 0.7 to 6.2) in the pemetrexed-plus-platinum chemotherapy group.

A total of 44 (25.6%) and 46 (26.9%) deaths, respectively, had been reported in the crizotinib and pemetrexed-plus-platinum chemotherapy groups as of the data cut-off date. With 68% of patients still in follow-up, the median OS was not reached in either arm. At the time of analysis, crizotinib treatment was not associated with statistically significantly longer survival compared with chemotherapy (hazard ratio [HR] 0.82 [95% confidence interval [CI]: 0.54 to 1.26]). This analysis was confounded by the high number of crossovers from the pemetrexed-plus-platinum chemotherapy arm to the crizotinib arm upon disease progression. The probability of 1-year survival was 84% (95% CI: 77 to 89) in the crizotinib group and 79% (95% CI: 71 to 84) in the pemetrexed-plus-platinum chemotherapy group.

The overall survival analysis was also adjusted using the rank-preserving structural failure time (RPSFT) adjustment technique to explore the effect of crossover to crizotinib in the pemetrexed-plus-platinum chemotherapy group. The resulting crossover adjusted hazard ratio for overall survival of crizotinib versus pemetrexed-plus-platinum chemotherapy was 0.60 (95% CI: 0.27 to 1.42) as calculated with the Wilcoxon Test and 0.67 (95% CI: 0.28 to 1.48) as calculated with the long-rank test. Median overall survival was not reached in either group.

Progression-free survival

Progression-free survival was the primary endpoint in PROFILE 1014. Crizotinib significantly prolonged progression-free survival compared with pemetrexed-plus-platinum chemotherapy, as determined by independent radiology review. The median progression-free survival was 10.9 months (100 events [58%]) for patients randomized to crizotinib and 7.0 months (137 events [80%]) for patients randomized to pemetrexed-plus-platinum chemotherapy. The hazard ratio comparing crizotinib with pemetrexed-plus-platinum chemotherapy was 0.45 (95% CI: 0.35 to 0.60) (Figure 1a Solomon et al 2014 NEJM[13]). Among patients randomly assigned to crizotinib, 74 of 89 patients with progressive disease (83%) continued to receive crizotinib beyond disease progression for a median of 3.0 months (range, 0.7 to 22.6).
Crizotinib significantly prolonged progression-free survival compared with pemetrexed-cisplatin, where the median progression-free survival was 10.9 months with crizotinib and 6.9 months with pemetrexed-cispatin, hazard ratio 0.49 (95% CI: 0.36 to 0.67). Crizotinib also significantly prolonged progression-free survival compared with pemetrexed-carboplatin, where the median progression-free survival was 10.9 months with crizotinib and 7.0 months with pemetrexed-carboplatin, hazard ratio 0.45 (95% CI: 0.32 to 0.62).

The treatment effect of crizotinib across pre-specified subgroups in PROFILE 1014 was estimated using Cox proportional hazards models and these effects were generally consistent with the primary analysis for progression-free survival (Table 6). The 95% confidence intervals for hazard ratio estimates were overlapping for patients with non-adenocarcinomas, but this may be partly due to the relatively small number of patients in this subgroup (n = 21). Patients with an ECOG performance status of 2 had a hazard ratio that favoured crizotinib more than patients with an ECOG performance status of 0 or 1, but the sample size for this subgroup was small (n = 18) and confidence intervals were wide. A subgroup analysis on EGFR mutation and prior adjuvant chemotherapy was not available as this information was not collected. The manufacturer's report did not indicate whether or not tests for interaction in subgroups were conducted.

Table 6: Progression-free Survival by Subgroup (Pre-specified According to the Systematic Review Protocol)[13]		
Subgroup	**Progression-free Survival***	
	Number of patients	**Hazard Ratio (95% CI) of Crizotinib versus Chemotherapy**
Primary analysis	343	0.45 [0.35 to 0.60]
Sex		
Male	131	0.54 [0.36 to 0.82]
Female	212	0.45 [0.32 to 0.63]
Race		
Asian	157	0.44 [0.30 to 0.65]
Non-Asian	186	0.53 [0.36 to 0.76]
ECOG performance status		
0/1	324	0.47 [0.36 to 0.62]
2	18	0.19 [0.05 to 0.76]
Smoking status		
Never smoker	218	0.41 [0.29 to 0.58]
Current smoker/Ex-smoker	125	0.64 [0.42 to 0.97]
Histologic subtype		
Adenocarcinoma	322	0.49 [0.37 to 0.64]
Non-adenocarcinoma	21	0.37 [0.12 to 1.10]
EGFR mutation†	Not applicable	Not applicable
Positive		
Negative		
Prior adjuvant chemotherapy†	Not applicable	Not applicable
Yes		
No		
CI = confidence interval; **ECOG** = Eastern Cooperative Oncology Group; **EGFR** = epidermal growth factor receptor		

* Based on independent radiology review (IRR) assessment.
† A subgroup analysis was not available as this information was not collected.

Quality of life

Baseline global quality of life, functioning, and symptom scores using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30) and the corresponding module for lung cancer (QLQ-LC13) scales were similar between the crizotinib and pemetrexed-plus-platinum chemotherapy groups in PROFILE 1014 (Table 3). Scores were assessed on days 7 and 15 of cycle 1, on day 1 of every subsequent cycle, and at the end of treatment. For global quality of life and functioning domains, higher scores indicate better global quality or life or functioning; therefore positive changes indicate improvement from baseline. For symptoms, higher scores indicate a greater severity of symptoms; therefore negative changes indicate an improvement from baseline. In most domains, the crizotinib group had an improvement from baseline, while the pemetrexed-plus-platinum chemotherapy group had a decline from baseline.

There was a statistically significantly greater overall improvement from baseline in global quality of life in patients treated with crizotinib compared with pemetrexed-plus-platinum chemotherapy ($p < 0.001$) (Figure 2a Solomon et al 2014 NEJM[13]). A clinically meaningful change from baseline in global quality of life was defined as a ≥ 10 point improvement, and this was achieved for cycles 9 and 10 in the crizotinib group, but not in the remaining cycles. The chemotherapy group experienced deterioration from baseline in global quality of life score, which exceeded 10 points

on day 7 and day 15 of cycle 1.[70] Crizotinib was also associated with a statistically significantly greater overall improvement from baseline in physical, social, emotional, and role functioning domains ($p < 0.0001$). There was a significantly greater overall reduction from baseline with crizotinib than with chemotherapy in the symptoms of pain, dyspnea, and insomnia ($p < 0.0001$) as assessed using the QLQ-C30 scale (Figure 2b Solomon et al 2014 NEJM[13]), and in the symptoms of dyspnea ($p < 0.0001$), cough ($p < 0.0001$), chest pain ($p < 0.0001$), arm or shoulder pain ($p = 0.0002$), and pain in other parts of the body ($p = 0.0001$) as assessed using the QLQ-LC13 scale ($p < 0.001$) (Figure 2c Solomon et al 2014 NEJM[13]). There was a significantly greater deterioration from baseline in diarrhea ($p < 0.0001$) and peripheral neuropathy ($p = 0.0427$) with crizotinib, and in fatigue ($p < 0.0001$), nausea and vomiting ($p = 0.0468$), appetite loss ($p < 0.0001$), and alopecia ($p = 0.0108$) with chemotherapy (Figure 2b and 2c Solomon et al 2014 NEJM[13]). No significant differences were found between crizotinib and pemetrexed-plus-platinum chemotherapy in overall change from baseline in constipation, hemoptysis, sore mouth, or dysphagia ($p > 0.05$).

The time to deterioration, defined as the first occurrence of a ≥ 10-point increase from baseline in a composite score of cough, dyspnea, and chest pain from the QLQ-L13, was statistically significantly longer in the crizotinib group compared to the pemetrexed-plus-platinum chemotherapy group (HR 0.62 [95% CI: 0.47 to 0.80]).

Objective response rate

In PROFILE 1014, the objective response rate for patients randomized to crizotinib was significantly higher with crizotinib than with chemotherapy (74.4% [95% CI: 67 to 81] vs. 45.0% [95% CI: 37 to 53]; P < 0.001). The median time to response was 1.4 months (range 0.6 to 9.5 months) in the crizotinib group and 2.8 months (range 1.2 to 8.5 months) in the chemotherapy group, while the median duration of response was 11.3 months (range 8.1 to 13.8 months) and 5.3 months (4.1 to 5.8 months), respectively.

Harms Outcomes

Serious adverse events

In PROFILE 1014, 44 deaths occurred among patients receiving crizotinib compared with 46 deaths among patients receiving chemotherapy. Among the 44 deaths in the crizotinib arm, 16 were due to disease progression (Table 7). The higher number of deaths due to disease progression in the crizotinib group compared to the pemetrexed-plus-platinum chemotherapy group may be due to the longer duration of treatment in the crizotinib group.

Overall, serious adverse events occurred in 33.9% of patients in the crizotinib group and 27.8% of patients in the pemetrexed-plus-platinum chemotherapy group. The most common serious adverse events occurring in at least 4% of patients in either arm included disease progression (crizotinib versus chemotherapy, 8.8% vs 0.6%), dyspnea (4.1% vs 2.4%), and pulmonary embolism (2.9% vs 4.1%).

Table 7: Grade 5 Adverse Events of Any Cause* by Treatment Group in PROFILE 1014, Safety Population[13]

AEs, n (%)	Crizotinib (n=171)	Chemotherapy (n=169)
Disease progression	16 (9.4)†	1 (0.6)
Septic shock	2 (1.2)	0
Acute respiratory failure	1 (0.6)	0
Diabetic ketoacidosis	1 (0.6)	0
Cardiac arrest	0	1 (0.6)
Completed suicide	0	1 (0.6)

Table 7: Grade 5 Adverse Events of Any Cause* by Treatment Group in PROFILE 1014, Safety Population[13]		
AEs, n (%)	**Crizotinib (n=171)**	**Chemotherapy (n=169)**
Hemoptysis	0	1 (0.6)

* Adverse events leading to death between treatment start and 28 days after the last administration of study drug (only events before crossover to crizotinib were included in the chemotherapy group)

†Two patients included although the event occurred >28 days after the last dose of crizotinib

Table 8: Serious Adverse Events (Occurring in ≥2% of Patients in Either Treatment Group) by Treatment Group in PROFILE 1014, Safety Population[13, 49]		
SAEs, n (%)	**Crizotinib (n=171)**	**Chemotherapy (n=169)**
Total SAEs	**58 (33.9)**	**47 (27.8)**
Disease progression	15 (8.8)	1 (0.6)
Dyspnea	7 (4.1)	4 (2.4)
Pulmonary embolism	5 (2.9)	7 (4.1)
Pleural effusion	2 (1.2)	5 (3.0)
Vomiting	2 (1.2)	4 (2.4)
Convulsions	0	5 (3.0)

Adverse events

Only events that occurred in the chemotherapy group prior to crossover to crizotinib were included. Rates were not adjusted for differences in treatment duration in each group.

The proportion of patients that experienced an adverse event of any grade was 99.4% in both crizotinib and pemetrexed-plus-platinum chemotherapy groups. Notable differences in reported AE percentages in PROFILE 1014 when comparing crizotinib versus chemotherapy treatment included vision disorder (71.3% versus 9.5%), diarrhea (61.4% versus 13.0%), edema (48.5% versus 12.4%), elevated aminotransferases (35.7% versus 13.0%), upper respiratory infection (32.2% versus 12.4%), dysgeusia (26.3% versus 5.3%), anemia (8.8% versus 32.0%), and thrombocytopenia (1.2% versus 18.3%).

The majority of events in both treatment groups were grade 1 or 2 in severity. Grade 3 to 4 adverse events were similar between the crizotinib and chemotherapy groups, except for elevated transaminases occurring in 14.0% of patients receiving crizotinib compared with 2.4% of patients receiving chemotherapy (Table 9). Four hepatic events resulted in permanent discontinuation of treatment in the crizotinib group. Three events involved elevated amino transferase levels only, and one event involved a drug-induced liver injury. No deaths from hepatic dysfunction occurred.

Table 9: Adverse Events (Occurring in ≥15% of Patients in Either Treatment Group) by Treatment Group in PROFILE 1014, Safety Population[13, 49]		
AEs, n (%)	**Crizotinib (n=171)**	**Chemotherapy (n=169)**
Total AEs	**170 (99.4)**	**168 (99.4)**
Vision disorder*	122 (71.3)	16 (9.5)
Diarrhea	105 (61.4)	22 (13.0)
Nausea	95 (55.6)	99 (58.6)
Edema*	83 (48.5)	21 (12.4)
Vomiting	78 (45.6)	60 (35.5)
Constipation	74 (43.3)	51 (30.2)
Elevated aminotransferases*	61 (35.7)	22 (13.0)
Decreased appetite	51 (29.8)	57 (33.7)

Table 9: Adverse Events (Occurring in ≥15% of Patients in Either Treatment Group) by Treatment Group in PROFILE 1014, Safety Population[13, 49]		
AEs, n (%)	**Crizotinib (n=171)**	**Chemotherapy (n=169)**
Upper respiratory infection*	55 (32.2)	21 (12.4)
Fatigue	49 (28.7)	65 (38.5)
Abdominal pain*	45 (26.3)	20 (11.8)
Dysgeusia	45 (26.3)	9 (5.3)
Cough*	39 (22.8)	33 (19.5)
Headache	37 (21.6)	25 (14.8)
Neutropenia*	36 (21.1)	51 (30.2)
Neuropathy*	35 (20.5)	2 (1.2)
Pyrexia	32 (18.7)	18 (10.7)
Dizziness*	31 (18.1)	17 (10.1)
Dyspnea*	30 (17.5)	26 (15.4)
Pain in extremity	27 (15.8)	12 (7.1)
Stomatitis*	24 (14.0)	34 (20.1)
Asthenia	22 (12.9)	41 (24.3)
Anemia*	15 (8.8)	54 (32.0)
Leukopenia*	12 (7.0)	26 (15.4)
Thrombocytopenia*	2 (1.2)	31 (18.3)

* Denotes pre-specified clustered terms

Table 10: Grade 3 and 4 Adverse Events (Occurring in ≥2% of Patients in Either Treatment Group) by Treatment Group in PROFILE 1014, Safety Population[13]		
AEs, n (%)	**Crizotinib (n=171)**	**Chemotherapy (n=169)**
Elevated transaminases*	24 (14.0)	4 (2.4)
Neutropenia*	19 (11.1)	26 (15.4)
Pulmonary embolism*	11 (6.4)	11 (6.5)
Dyspnea*	5 (2.9)	4 (2.4)
Fatigue	5 (2.9)	4 (2.4)
Decreased appetite	4 (2.3)	1 (0.6)
Diarrhea	4 (2.3)	1 (0.6)
Electrocardiogram QT prolonged	4 (2.3)	0
Hypophosphatemia	4 (2.3)	2 (1.2)
Pneumonia	4 (2.3)	2 (1.2)
Leukopenia*	3 (1.8)	9 (5.3)
Hypokalemia	3 (1.8)	4 (2.4)
Vomiting	3 (1.8)	5 (3.0)
Hyponatremia	1 (0.6)	4 (2.4)
Anemia*	0	15 (8.9)
Thrombocytopenia*	0	11 (6.5)

* Denotes pre-specified clustered terms

Withdrawals due to adverse events[49]

A total of 12.3% (21/171) of patients in the crizotinib group and 14.2% (24/169) of patients in the chemotherapy group permanently discontinued treatment due to an adverse event. The most

frequent adverse events that led to withdrawal in the crizotinib group were disease progression (4.1%, 7/171), elevated transaminases (1.2%, 2/171), hepatotoxity (1.2%, 2/171), and interstitial lung disease (1.2%, 2/171). The most frequent adverse events that led to withdrawal in the pemetrexed-plus-platinum chemotherapy group were blood creatinine increased (1.2%, 2/169), fatigue (1.2%, 2/169), pulmonary embolism (1.2%, 2/169), and thrombocytopenia (1.2%, 2/169).

6.4 Ongoing Trials

One ongoing manufacturer-funded trial was identified that is being conducted specifically in East Asian patients. Study A8081029 (NCT01639001 is a phase III, randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed-plus-platinum (cisplatin or carboplatin) in previously untreated East Asian patients with non-squamous NSCLC whose tumors harbor a translocation or inversion event involving the ALK gene locus. The study is expected to enroll at least 200 patients and has an estimated primary completion date of June 2015 (final data collection date for primary outcome measure – progression free survival) and an estimated study completion date of July 2017.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of crizotinib (Xalkori) for ALK-positive advanced or metastatic non-small cell lung cancer:

- Summary of ALK mutation testing in advanced or metastatic non-small cell lung cancer

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

7.1 Summary of ALK Mutation Testing in Advanced or Metastatic Non-small Cell Lung Cancer

7.1.1 Objective

To summarize ALK mutation testing and its role in identifying advanced or metastatic NSCLC patients who may be treated with crizotinib.

The provincial advisory group (PAG) is interested in the implementation and additional costs of ALK mutation testing, including different test methods available, cost differences, differences with respect to the level of evidence to support them, and issues associated with test accessibility (See Section 5 of the report).

7.1.2 Findings

Crizotinib is indicated for use specifically in patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours harbour an anaplastic lymphoma kinase (ALK) gene rearrangement.[15] It has been reported that ALK mutations may be seen in approximately 4% of the NSCLC population, and tests to identify this specific driver mutation allow the use of drugs that specifically target and exploit the mutation to improve clinical outcome, including the extension of time to disease progression and lengthening of overall survival, compared to standard chemotherapy options.[50] Fluorescent in situ hybridization (FISH) is the accepted gold standard technique for ALK testing. Screening with immunohistochemistry (IHC) goes on at centres across Canada with FISH confirmation of positive cases.[51] Other emerging techniques for ALK testing include chromogenic in situ hybridization (CISH), and reverse transcription–polymerase chain reaction (RT-PCR).

7.1.3 Description of a FISH Assay: The Vysis ALK Break Apart FISH Probe Kit

Currently, the Vysis ALK Break Apart FISH Probe Kit (here also referred to as 'ALK FISH') is the only companion diagnostic test approved by Health Canada to detect rearrangements involving the ALK gene. The kit is manufactured by Abbott Molecular Inc,[16] and it was utilized to identify ALK rearrangements in NSCLC patients in Phase II and III crizotinib trials.[31,52-58] ALK FISH test is performed using slides prepared from formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens.[59] Since FFPE is the most common method for processing and storing tumor specimens in pathology laboratories,[16] it affords availability of tumor tissue suitable for the test to the majority of NSCLC patients. However, according to the manufacturer, assay using the ALK FISH should be performed only on 10% neutral buffered formalin FFPE human lung cancer tissue for which it has been optimized. Other types of specimens or fixatives should not be used. One unstained slide cut from the FFPE block is sufficient for ALK FISH testing.[16]

The following materials are included in the probe kit provided by the manufacturer:[59,60]

1) Vysis LSI ALK Dual Colour Break Apart FISH Probe (1 vial, 200 µL per vial). The ALK Break Apart probe set includes two fluorophore-labeled DNA probes: Vysis LSI 3'-ALK SpectrumOrange and Vysis LSI 5'-ALK SpectrumGreen.

2) DAPI I Counterstain (1 vial, 300 µL per vial), 1 µg/10 mL in phenylenediamine dihydrochloride, glycerol, and phosphate buffered saline mixture.

There are additional reagents and materials that are required for the conduct of the test, but not included in the kit, most notably:

1) Vysis Paraffin Pretreatment IV & Post-Hybridization Wash Buffer Kit

2) ProbChek ALK Negative Control Slides

3) ProbChek ALK Positive Control Slides

A single ALK- FISH kit can analyze up to 10 samples (9 patient samples plus 1 control) per hybridization.

The FISH technique allows the visualization of specific chromosome nucleic acid sequences within a cellular preparation by using fluorophore-labeled DNA probe to complementary target sequences in a precisely annealed single-stranded from the DNA of test cells. Fluorescence microscopy is used to visualize the hybridization of the probe with the cellular DNA region. For a reliable determination of ALK mutation status using FISH testing, the target viewing area must contain a minimum of 50 evaluable cells.[61]

In a cell without ALK rearrangement, hybridization with FISH probes shows as two immediately adjacent or fused orange/green signals. A cell with ALK chromosome rearrangement presents one orange and one green signal separated by at least two signal diameters. Alternatively, a single orange signal (deletion of green signal) in addition to a fused or broken apart signal may be seen.[61] Thus negative and positive ALK rearrangement in NSCLC using ALK FISH test may be summarized as follows:

Negative (non-rearranged) when:

- Orange and green signals are adjacent or fused or
- There is a single green signal without a corresponding orange signal

Positive (re-arranged) when:

- At least one set of orange and green signals are two or more signal diameters apart, or
- There is a single orange signal without a corresponding green signal in addition to fused and/or broken apart signals.

The number of fused (adjacent) signals, as well as the of single orange and single green signals are recorded for each nucleus, without scoring nuclei with no signals or with signals of only one color without a fused and/or broken apart signal. The number of cells considered as negative or positive are determined and used to classify a sample.

A sample is considered decidedly negative, if < 5 cells out of 50 (<10%) are positive. If a sample has > 25 positive cells out of 50, it is conclusively ALK positive. The classification of a sample with 10 to 50% of positive cells is considered equivocal requiring a second reader evaluate the slide. In this case, a percent is calculated from the sum the first and second cell counts readings and a determination is made as follows:

- average percent positive cells < 15%, the sample is considered negative.
- average percent positive cells ≥ 15%, the sample is considered positive.[61]

The reproducibility of the Vysis ALK Break Apart FISH Probe Kit has been evaluated in external laboratories with reported overall percent agreement between all reader results of 97.64% (95% CI 96.25 – 98.52). The positive percent agreement (was 96.46% (95% CI 94.40 – 97.78) and the negative percent agreement was 100.00% (95% CI 98.42 – 100.00). The overall kappa coefficient was 0.92 (95% CI 0.85 – 0.98) with a Z-Score of 27.08. The kappa coefficient demonstrated the reproducibility for each site, ranging from 0.83 to 0.96, and for each lot, ranging from 0.86 to 0.96.[61]

The most important advantage of ALK FISH is that it is capable of detecting any ALK rearrangements, including potentially rare or uncharacterized ALK rearrangements.[16]

The use of FISH as a routine screening method for ALK-rearranged NSCLC has limitation in high cost and the fact it is not feasible in all laboratories. ALK FISH requires appropriated optical filters for its probes, and the fluorescence microscope to detect the fluorescent split signal is not routinely used in pathology. Also, the green signal may fade earlier than the red signal, increasing the likelihood of false-positive single-red signals. In addition, the break apart red and green signals indicating ALK rearrangements can be subtle and sometimes difficult to recognize.[62] At the moment, the ALK FISH diagnostic has limited automation, the results are not always clear, and the interpretation is complex. Therefore, it is preferable that the results should be interpreted by a pathologist. Although well trained and experienced persons in histo- and cytomorphology could score the specimens, a pathologist should coordinate, validate, review and sign off the interpretation when this happens.[62] The results of hybridization takes about 48 hours to obtain.

7.1.3.1 Other Assays to Identify ALK Gene Rearrangements: IHC, CISH, and RT-PCR

Immunohistochemical(IHC) detection of the ALK rearrangement

The biological bases of IHC to detect ALK rearrangements in NSCLC is that over-expression of the ALK protein occurs following the translocation or inversion of part of the ALK gene leading to overactivity of the ALK tyrosine kinase.[62] For crizotinib in particular, IHC seems a logical test since the drug targets the ALK tyrosine kinase protein.

Currently, there are three primary antibodies commonly referred to in the published literature; clone 5A4 (Novocastra, Leica, but also available pre-diluted from Abcam), ALK1 (Dako) and D5F3 (Cell Signalling Technology). There is currently no literature with conclusive evidence about the comparative advantage of one of these antibodies over the other. However, literature has reported variation in the best concentrations of various primary antibodies and the antigen retrieval methodology.[62] The use of these antibodies has very high negative predictive value, with all IHC-negative cases also being FISH-negative, and they have also resulted in high probability (90–100 %) of being FISH positive when IHC is strongly positive (+++).[62]

Detection of ALK rearrangement using IHC is done through scoring the degree and character of cytoplasmic staining following treatment with the appropriate reagents. Assessment of staining intensity is very subjective. The modified H-score which use successive microscope objectives with related spatial resolutions as a physical aid in establishing intensity is recommended. Strong staining (+++) is clearly visible using a ×2 or ×4 objective, moderate staining (++) requires a ×10 or ×20 objective to be clearly seen, whilst weak staining (+) cannot be seen until a ×40 objective is used.

A prospective study by pan-Canadian ALK diagnostic project (CALK) the 5A4 (Novocastra) or ALK-1 (Dako) antibodies found IHC sensitivity and specificity of 100% and 91.8 %, respectively

compared to FISH and concluded that the finding supported IHC as a reliable method to screen for ALK-rearranged lung cancers.[63] They also suggest that a clearly positive IHC result may be used to determine ALK status.[63] In another study by CALK using 5A4 antibody, it was found that except for one discrepant case with atypical FISH finding of unknown clinical implication, IHC detected all FISH-positive ALK tumors. The report concluded that standardization across multiple centres for ALK testing using IHC and FISH can be achieved.[64] The CALK was initiated in 2011 to validate ALK detection methods and standardizing ALK assays in Canada.[65]

At the time of this pCODR review, however, IHC was not yet clinically validated and, unlike FISH ALK, it has not been licenced by Health Canada to be used to screen for AKL rearrangement in NSCLC. This notwithstanding, IHC screening with is used at centres across Canada for initial diagnostic detection of ALK rearrangements with positive test confirmed with FISH.

The advantages IHC include the fact that it is an affordable method which is familiar to pathologists, and easily to integrate into a diagnostic protocol. It is a rapid, mostly automated assay that can analyze from 30 to 60 samples (depending on the autostainer) producing results in three to five hours compared to the several weeks required to obtain results from a FISH test. The assay is easy to read by pathologists and is semi-quantitative with signal scores ranging of 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong).[16] However, because the protein concentrations in ALK-rearranged NSCLC are relatively low, standard detection methodology is inadequate for the detection of all cases of ALK-rearranged NSCLC. Thus detection methodology with signal enhancement system may be required. Furthermore, variation in the best concentrations of various primary antibodies and the antigen retrieval methodology may be a limitation just as the absence of a standardized the scoring system.[62] In addition, IHC is sensitive to tissue fixation, which could lead to false-negative results and decreased sensitivity in detecting ALK arrangements.[16]

Chromogenic in situ hybridization (CISH)

CISH for ALK gene rearrangement detection is a relatively new assay in which the DNA probe is detected using an immunoperoxidase (chromogenic) reaction. This method is very close to FISH, but it does not require the use of fluorescence microscopy. Thus, it may overcome some of the disadvantages of ALK FISH as it allows easier quantification of the chromogen signals by conventional bright field light microscopy.[66] In addition, CISH is a fully automated assay and it provides stable and permanent archival slides. However, there is a paucity of data on the use of CISH for determining ALK status. Kim et al. compared CISH with FISH by measuring the ALK gene rearrangement status of 465 consecutive FFPE NSCLC samples.[66] Results from both assays were correlated with protein expression by IHC (clone 5A4, Novocastra) and slides were read and interpreted by two independent pathologists. Kim et al. reported agreement between the pathologists using CISH was achieved in 449 samples (96.6%) versus 453 samples (97.4%) using FISH, and ALK rearrangement was identified in 18 samples (4.0%) with CISH versus 19 (4.2) with FISH. There was high concordance in the assessment of ALK gene rearrangement between the FISH and CISH techniques ($\kappa = 0.92$) and between observers ($\kappa = 0.97$). When FISH was chosen as the gold standard, the sensitivity and specificity of CISH were 94.4% and 100%, respectively (positive predictive value 100%, negative predictive value 99.8%).[66] There was only one discordant case between FISH and CISH. In addition, there was high concordance in the ALK gene status and ALK protein expression between CISH and IHC tests ($\kappa = 0.82$). Therefore, CISH appears to be a useful technique for determining ALK status. However, further research, including clinical validation is necessary to fully evaluate CISH as a routine method of determining ALK status.

Reverse transcription–polymerase chain reaction (RT-PCR)

RT-PCR of cDNA is another commonly used screening strategy for detecting ALK gene rearrangements in NSCLC. However, the assay typically requires RNA extraction from fresh-frozen tissue samples, which are not routinely available in laboratory practice. As RNA is more sensitive to degradation than DNA or protein, compared with FISH or IHC, this test is more likely to fail or leads to false-positive results due to contaminations. In addition, RT-PCR cannot identify previously uncharacterized novel rearrangements.[16]

7.1.4 Implementation of ALK Mutation Tests

The importance of a country-wide adoption for molecular diagnosis to foster effective biomarker-directed therapy of lung cancer in Canada has received significant advocacy in the oncology community in recent years.[51,67,68] The advantages of treatment approach includes significantly improved treatment outcomes, including response, quality of life and progression-free survival, and in some cases may even improve overall survival, among patients suitable matched to therapy following effective screening. In addition to superior treatment benefits, biomarker driven personalized therapy protect patients from adverse events due to medication they do not need, and the potential to help oncologist select alternatives for patients who otherwise would have been unsuitable candidates for standard chemotherapy.

Despite these and other advantages, there is currently no standardized molecular testing protocol in Canada for ALK rearranged NSCLC integrated into the routine diagnosis of lung cancer. In fact no such protocol exists for other forms of lung cancer. Barriers hindering the implementation of knowledge and evidence-based proposed policies include lack of integration of biomarker testing into routine pathology practice, lack of knowledge dissemination to involved specialties (beyond medical oncology and academic pathology), absence of specific or sufficient funding for biomarker testing, and insufficient tumour samples for testing.[51]

National groups such as Community Academic Research Exchange (CARE) working with multidisciplinary health care providers throughout Canada have proposed early and reflexive molecular testing to improve the likelihood of the result being available at the time of the initial consultation with the medical oncologist and thus prevent delays in initiating effective therapy.[50]

According to the Policy on Molecular Testing in lung Cancer document published by Lung Cancer Canada (LCC) in 2014, the cost of a proposed reflex model for testing ALK and EGFR in Manitoba is projected to be $227,595.00 annually. The initial IHC-ALK test and the FISH confirmation components of this cost are $13,500.00 and $24,700.00, respectively (see Figure). Although, a comprehensive national estimate of the cost of IHC-ALK and confirmatory FISH tests could not be found through our literature search, these figures may facilitate a not-so-rigorous projection based on national incidence of NSCLC and the already reported approximately 4% of ALK rearranged cases among this population. However, this is outside the scope of the Supplemental Question.

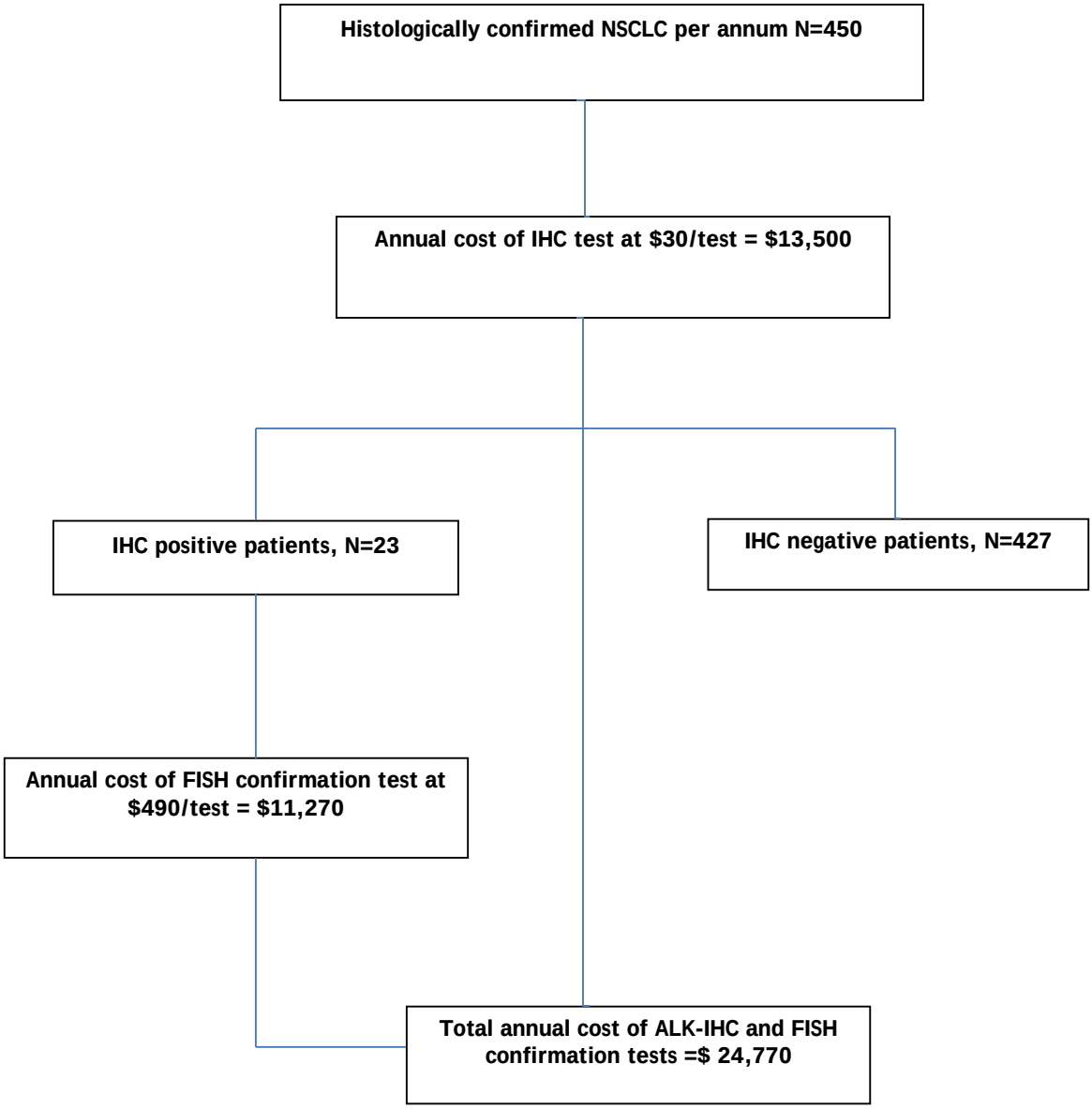


Figure 1: Annual cost of preliminary ALK-IHC screening and FISH confirmation test in histologically confirmed NSCLC patients in Manitoba. Adapted from the proposed testing algorithm from ALK and EGFR testing in Manitoba using the reflex model.[67]

7.1.5 Summary

Currently, the Vysis ALK Break Apart FISH Probe Kit is the only diagnostic assay with regulatory approval for identifying ALK-positive NSCLC patients to receive targeted systemic therapy with crizotinib.[15] ALK FISH test is the current gold standard and it is capable of detecting any ALK rearrangements including potentially rare, uncharacterized ALK rearrangements. The test is conducted on FFPE lung cancer tissue with either resection or cytology specimens. One unstained slide cut from the FFPE block is sufficient for ALK FISH testing.[16] However, the conduct and interpretation of the test results require special technical training and it is not feasible in all laboratories Canada. Other diagnostic assays such as IHC, CISH and RT-PCR are available although they have not been standardized and clinically validated in large multicentre studies to screen for ALK-positive NSCLC patients. The CALK project has reported IHC sensitivity and specificity of 100% and 91.8 %, respectively compared to

FISH. It was concluded that the finding supported IHC as a reliable method to screen for ALK-rearranged NSCLC.[63] Another CALK study concluded that standardization across multiple centres for ALK testing using IHC and FISH can be achieved. Although a standardized ALK status screening integrated with NSCLC diagnostic procedure is not currently available in Canada, a two-tiered protocol with preliminary IHC-positive diagnostic detection followed by FISH confirmation test is used at centres across Canada to identify ALK-positive NSCLC patients.[17-20]

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on crizotinib for advanced non-small cell lung cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. Personal identifying information has been removed from the registered patient advocacy group section, to the Clinical Guidance Report.

This Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Lung Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY [AUTHOR: Methods Team]

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2015, **Embase** 1974 to 2015 February 26, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	(Crizotinib* or Xalkori* or "PF 02341066" or PF2341066 or PF02341066 or PF 2341066 or 877399-52-5).ti,ab,ot,sh,hw,rn,nm,kw.	3383
2	1 use pmez,cctr	706
3	*crizotinib/ or *"3 [1 (2,6 dichloro 3 fluorophenyl)ethoxy] 5 [1 (4 piperidinyl) 1h pyrazol 4 yl] 2 pyridinylamine"/ or (Crizotinib* or Xalkori* or "PF 02341066" or PF02341066 or PF2341066 or PF 2341066 or 877399-52-5).ti,ab.	2025
4	3 use oemezd	1402
5	2 or 4	2108
6	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	899484
7	Randomized Controlled Trial/	749040
8	Randomized Controlled Trials as Topic/	167346
9	"Randomized Controlled Trial (topic)"/	66104
10	Controlled Clinical Trial/	479071
11	Controlled Clinical Trials as Topic/	8791
12	"Controlled Clinical Trial (topic)"/	3714
13	Randomization/	167465
14	Random Allocation/	167465
15	Double-Blind Method/	353856
16	Double Blind Procedure/	120559
17	Double-Blind Studies/	315076
18	Single-Blind Method/	52096

19	Single Blind Procedure/	19568
20	Single-Blind Studies/	52096
21	Placebos/	319812
22	Placebo/	265513
23	Control Groups/	73271
24	Control Group/	73183
25	(random* or sham or placebo*).ti,ab,hw.	2839205
26	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	589067
27	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1415
28	(control* adj3 (study or studies or trial*)).ti,ab.	918092
29	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	67761
30	allocated.ti,ab,hw.	118250
31	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	66703
32	or/6-31	3595170
33	5 and 32	217
34	exp animals/	38051719
35	exp animal experimentation/ or exp animal experiment/	1840832
36	exp models animal/	1241196
37	nonhuman/	4458761
38	exp vertebrate/ or exp vertebrates/	37091020
39	or/34-38	39325666
40	exp humans/	29718319
41	exp human experimentation/ or exp human experiment/	346391
42	or/40-41	29720397
43	39 not 42	9606854
44	33 not 43	213

45	limit 44 to english language	208
46	remove duplicates from 45	186

2. Literature search via PubMed

Search	Query	Items found
#1	Search **(Crizotinib OR Xalkori OR "PF 02341066" [tiab] OR PF2341066 [tiab] OR PF02341066 [tiab] OR "PF 2341066" [tiab]) AND publisher [sb]**	40

Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid (see section 1 above)

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

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

Search terms: Xalkori/crizotinib + lung neoplasms

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

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

Search terms: Xalkori/crizotinib

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncolody (ESM0)
http://www.esmo.org/

Search terms: Xalkori/crizotinib + NSCLC last 5 years

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