pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

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

September 19, 2014

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FUNDING

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

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1 GUIDANCE IN BRIEF

1.1 Background

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

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

PROFILE 1007 was an open-label, multicentre, randomized, phase 3 trial of crizotinib versus second-line standard of care chemotherapy, pemetrexed or docetaxel, in ALK-positive, advanced NSCLC patients who received one prior chemotherapy regimen that was platinum-based. Data from 1007 were the focus of the resubmission systematic review.

Patients in PROFILE 1007 were randomized 1:1 to crizotinib or chemotherapy (n=173 and n=174, respectively), stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The first choice for patients randomized to chemotherapy was pemetrexed unless patients received pemetrexed as part of their prior therapy or had squamous histology. Patients treated with chemotherapy who had disease progression had the option to switch treatment and receive crizotinib in a separate trial (study 1005).

The primary outcome was progression-free survival according to RECIST v1.1-defined disease progression as determined by independent radiology review, unacceptable toxicity, consent withdrawal, or death. The primary endpoint was achieved with a median progression-free survival of 7.7 months (100 events [58%]) for patients randomized to crizotinib and 3.0 months (127 events [73%]) for patients randomized to chemotherapy. The hazard ratio comparing crizotinib with chemotherapy was 0.49 (95% CI: 0.37 to 0.64).

Key secondary outcomes of PROFILE 1007 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 chemotherapy. The objective response rate was also significantly better for patients randomized to crizotinib (65.3% [95% CI: 58 to 72]) as compared with chemotherapy (19.5% [95% CI: 14 to 26]). The prespecified interim overall survival analysis did not show a statistically significant benefit in favour of crizotinib. Median overall survival was estimated to be 20.3 months for crizotinib versus 22.8 months for chemotherapy (hazard ratio 1.02 [95% CI: 0.68 to 1.54]). However, 112 (64%) patients crossed over from the chemotherapy arm to crizotinib upon disease progression, thereby confounding the overall survival analysis. A post hoc analysis adjusting for crossovers suggested a trend in survival benefit with crizotinib over chemotherapy, but this was also not statistically significant.

Crizotinib was associated with a statistically significantly greater improvement from baseline in global quality of life in patients treated with crizotinib compared with chemotherapy (estimated difference 9.84, 95% CI: 5.39–14.28) and a statistically significant greater improvement from baseline in symptoms and functioning (except for cognitive functioning) on the EORTC QLQ-C30/QLQ-LC13 compared with chemotherapy.

Harms outcomes in the crizotinib group of 1007 were consistent with those reported in the original pCODR systematic review. SAEs occurred in 37.2% and 23.4% of patients receiving

crizotinib and chemotherapy, respectively. SAEs occurring in at least 5% of patients in the crizotinib versus chemotherapy arm included disease progression (7.6% versus 1.8%) and neutropenia (1.7% versus 8.2%).

Although limitations are associated with drawing conclusions from data extracted from non-peer reviewed sources (except for the published article with updated 1001 data[1]), updated efficacy and safety data from PROFILE 1001 and 1005 were consistent with what was presented in the original pCODR systematic review.

Two ongoing phase one/two multicentre, multinational, open-label, single-arm trials, PROFILE1001 and PROFILE1005 evaluating the efficacy and safety of crizotinib 250 mg orally twice daily in treating ALK-positive NSCLC were included in the original pCODR systematic review.[2-9] The primary endpoint for both studies was objective response rate as evaluated by the investigator, with confirmatory assessment conducted by an independent review committee. Overall survival was a secondary outcome in both 1005 and 1001, but median overall survival has not been reached. Data on patient-reported outcomes using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, the lung version, from study 1005 were presented at the American Society of Clinical Oncology conference in 2011.[8] New data were provided following the resubmission that included updated efficacy and safety information on the two studies. Updated efficacy and safety data from PROFILE 1001 and 1005 were consistent with what was presented in the original pCODR systematic review.

1.2.2 Additional Evidence

pCODR received input on the original pCODR submission for crizotinib from one patient advocacy group, Lung Cancer Canada. Provincial Advisory Group input was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of crizotinib and is discussed as supporting information:

- Summary of ALK Mutation Testing

Li et al.[10] 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.[11] However, the review did not include the Li et al.[10] study likely because both were published in the same year (2012). Additional non-systematic reviews[12,13] have likewise indicated a lack of literature and evidence demonstrating progression-free survival as a valid surrogate for 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.[14] It is estimated that in 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 population, respectively.[15]

The phase I/II and phase II trials demonstrate the significant efficacy of crizotinib in achieving tumour responses in ALK-positive advanced or metastatic NSCLC. Benefits in terms of progression-free, overall survival and QoL compared to historical outcomes for the general population of advanced/metastatic NSCLC with unknown ALK mutation status are acknowledged.

PROFILE 1007 demonstrated a significant improvement in progression-free survival in favour of crizotinib vs cytotoxic chemotherapy (HR 0.49 (95% CI: 0.37-0.64)). However at this time, no overall survival benefit is evident, likely due to the crossover from chemotherapy to crizotinib that confounds this analysis. QoL benefits from treatment with crizotinib reflect the antitumour activity of the agent and its relatively modest toxicity profile.

Targeting a driver mutation such as ALK with crizotinib appears to be a successful treatment strategy, which is supported by the consistent tumour response rates for crizotinib reported between the two trials and the various subgroup comparisons, including gender, performance status, smoking status, and lines of prior therapy.

The tumour response rates seen with crizotinib in ALK-positive NSCLC are significantly greater than what is typically seen with existing standard systemic therapy, regardless of mechanism of action and the line of treatment. The clinical parameters such as gender, performance status and smoking status do not predict response to crizotinib highlights the importance of EML4-ALK companion laboratory testing to establish ALK mutation status for the selection of the appropriate treatment population.

The safety profile of crizotinib appears favourable, with the spectrum and incidence of adverse effects in keeping with other oral molecularly targeted agents used in the management of NSCLC. The frequency of adverse effects leading to discontinuation of treatment in the two reported trials was low.

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

Improvement in progression-free survival and QoL is felt to be of sufficient benefit to support use of this therapy, particularly as it is associated with modest treatment-related toxicity. Thus crizotinib appears to be a superior alternative to standard single-agent chemotherapy as second-line systemic therapy in advanced/metastatic NSCLC.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC as second-line systemic therapy. Crizotinib has demonstrated a clear clinically and statistically significant benefit in terms of progression-free survival compared to standard second-line chemotherapy in one Phase III randomised study.

The Clinical Guidance Panel also acknowledges the consistency of antitumour activity of crizotinib among the trials that have been reported to date. At present, limited follow up and crossover as a potential confounding factor in the phase III trial limits the assessment of crizotinib's impact on overall survival.

With establishment of appropriate routine companion ALK mutation testing, the panel felt it is the preferred option for ALK-positive advanced/metastatic patients to have access to crizotinib as second-line systemic therapy. The results of pending trials may clarify the role of crizotinib in other lines of therapy.

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.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature 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).[16] 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.[17,18]

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.[19] 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.

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 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.

The efficacy and safety of crizotinib 250 mg orally twice daily in treating ALK-positive NSCLC were examined in two ongoing phase 1/2 multicentre, multinational, open-label, single-arm trials, PROFILE1001 and PROFILE1005.[2-9]

Study 1005 was a phase 2 trial that enrolled patients with histologically or cytologically proven diagnosis of (locally advanced or metastatic) NSCLC that was positive for translocation or inversion events involving the ALK gene locus (based on Vysis ALK break apart fluorescence in situ hybridization [FISH] assay). Patients were also included if they: (1) were randomized into the chemotherapy group (pemetrexed or docetaxel) of the ongoing phase 3 second-line therapy study A8081007 and progressed on treatment; (2) had received prior chemotherapy and were ineligible for study A8081007; (3) had Eastern Cooperative Oncology Group (ECOG) performance status ≤3; or (4) had adequate organ function.[8,9,20,21]

Study 1001 was a two-part phase 1/2 trial, originally designed as a phase 1 dose-escalation study in patients with any tumor type (except leukemia) to evaluate the safety and pharmacokinetics of the maximum tolerated dose of crizotinib. However, an expanded cohort (recommended phase 2 dose cohort) enrolling patients with ALK-positive NSCLC was established following evidence of "dramatic improvement in symptoms"[2] among patients with ALK-positive NSCLC treated with crizotinib.[2,4-7,20,21] The recommended phase 2 dose cohort study was a multicenter, multinational, open-label, safety and efficacy study that included patients with histologically confirmed advanced malignancies harbouring ALK gene rearrangements (including ALK-positive NSCLC), MET amplification or activating mutations, or ROS gene rearrangements.

Owing to the paucity of published data on these studies, the U.S. FDA medical and statistical reviews were the primary sources for data extraction for this systematic review.[20,21] The original crizotinib regulatory submission to the FDA included data with cutoff dates of September 15, 2010 and 60-day clinical data updates as of February 1, 2011 for both studies. As of the study cutoff dates, the median duration of treatment was 22.3 (range: 0.9 to 53.1) weeks and 31.8 (range: 0.9 to 101.7) weeks in 1005 and 1001 for all treated patients, respectively.

Studies 1005 and 1001 treated 136 and 119 patients with ALK-positive NSCLC, respectively. Median age was 52 years on 1005 and 51 years on 1001.[20,21] The female/male ratio was similar on both studies with 47% and 50% male, respectively. The majority of the patients had an ECOG performance status of ≤1, were non- or former smokers with adenocarcinoma the predominant histological type in both studies. Only 15 patients in study 1001 had no prior systemic treatments and, thus, received crizotinib as first-line treatment.

The primary efficacy endpoint for both studies was objective response rate as rated by the investigators. Confirmatory assessment was conducted by an independent review committee. According to the FDA medical review,[20] 135 patients with ALK-positive advanced NSCLC from study 1005 and 116 from study 1001 were evaluable at the time of data cutoff. Based on the investigator assessments, the objective response rate was 49.6% (1 complete and 67 partial responses) from study 1005, and 61.2% (2 complete and 69 partial responses) from study 1001. The objective responses by independent review from studies 1005 and 1001 were 41.9% (1 complete and 43 partial responses) and 52.4% (0 complete and 55 partial responses), respectively. The median response duration ranged from 41.9 to 48.1 weeks among investigator assessed tumours versus 33.1 to 58.1 weeks among independently reviewed tumours.[20] On subgroup analysis (baseline treatment status for advanced/metastatic NSCLC; histologic type; ECOG performance status; sex; smoking status; and EGFR mutation status), there was no clear difference in objective response rates from either study,[20] although the small sample sizes within groups makes it difficult to draw conclusions from this analysis.

Overall survival was a secondary outcome in both 1005 and 1001, but median overall survival has not been reached. Preliminary results from 136 patients enrolled in study 1001 with a median follow-up time of 14.8 months indicated a 12-month survival probability of 75.7% (95% CI: 66.8 to 82.5).[21] Additional survival analyses were conducted in a retrospective study by Shaw et al. on the first 82 patients treated in study 1001.[3] Out of several subcohort analyses, the most relevant comparison was between ALK-positive/crizotinib-treated patients from 1001 who received crizotinib in the second- or third-line (n = 30) versus ALK-positive/crizotinib-naïve historical controls who had received any second-line therapy (n = 23). Survival among the ALK-positive/crizotinib patients was significantly longer than in ALK-positive/controls (hazard ratio 0.36 [95% CI: 0.17 to 0.75]; P = 0.004). However, given the non-randomized, retrospective study design and the very small number of patients per group, these results should be considered exploratory.

No published quality of life outcomes associated with crizotinib for advanced ALK-positive NSCLC were identified. The FDA review of crizotinib also did not describe the impact of crizotinib on quality of life in this population. Data on patient-reported outcomes – using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, the lung version, from study 1005 were presented at the American Society of Clinical Oncology conference in 2011.[8] Only 80% (109 out of 136 patients) of patients were evaluated; however, over the median nine weeks of treatment a clinically significant improvement (≥10 point improvement) in pain, cough, dyspnea, and fatigue was reported. A clinically significant increase in constipation was also reported by patients.[8] However, the limited details provided in the abstract prevent a full description and critical assessment of this data.

According to the FDA medical review,[20] 45 deaths occurred among patients receiving crizotinib in studies 1005 and 1001 combined, primarily due to disease progression. Adverse events that occurred within 28 days of crizotinib administration and that were associated death were largely respiratory-related. Nonfatal serious adverse events occurred in 24.3% of patients receiving crizotinib in studies 1005 and 1001 combined. Grade 3 to 4 adverse events occurred in 40.8% of the 255 patients in both studies. Events that occurred in greater than five percent of patients included elevated liver transaminases (AST/ALT), dyspnea, pneumonia, and neutropenia.[20] Among adverse events of any grade occurring in ≥25% of

patients, gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation) were the most commonly reported in both studies.[20] Visual disorders were also frequently reported (163 out of 255), mostly of grade 1 severity with no need for dose discontinuation or reduction.

Several key limitations of the reviewed studies should be considered. First, the single-arm, non-randomized, unblinded designs makes interpreting the efficacy and safety results difficult, especially when assessing more subjective outcomes such as response rate and progression-free survival. This can be illustrated by the difference in response estimates between the investigator assessed tumour response rate and the independent review estimates, where inter-rater agreement rates were 73.5% and 81.9% for studies 1005 and 1001, respectively.[22] Second, the appropriateness of objective response rate as a surrogate trial endpoint for overall survival in advanced NSCLC is unclear (see section 2.1.4 for more detail). However, the magnitude of the objective response rate in both trials was substantial, and evidence suggests that large response differences might be more predictive of a survival benefit.[23] Finally, ECOG performance status in both studies was predominantly ≤1. Performance status is a well-established prognostic factor in advanced NSCLC. Consequently, the beneficial effects of crizotinib may have been overestimated among a study population with better survival probabilities than typically seen in practice.

Resubmission New Data Summary

Five reports presenting new data from three studies were submitted by the manufacturer: updated results from 1001 (Camidge et al.[1], also identified in the pCODR literature search) and 1005 (2 conference abstracts[24]); and data from PROFILE1007 (conference abstract and top-line summary report;[24]), an open-label, multicentre, randomized, phase 3 trial of crizotinib versus second-line standard of care chemotherapy, pemetrexed or docetaxel, in ALK-positive, advanced NSCLC patients who received one prior chemotherapy regimen that was platinum-based. Data from the 1007 were the focus of the resubmission systematic review.

Patients in the 1007 were randomized 1:1 to crizotinib (n=173) or chemotherapy (n=174), stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The first choice for patients randomized to chemotherapy was pemetrexed unless patients received pemetrexed as part of their prior therapy or had squamous histology. The primary outcome was progression-free survival according to RECIST v1.1-defined disease progression as determined by independent radiology review, unacceptable toxicity, consent withdrawal, or death. Patients treated with chemotherapy who had disease progression had the option to switch treatment and receive crizotinib in a separate trial (study 1005). Key secondary outcomes of the 1007 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 chemotherapy.

Demographic and baseline characteristics were balanced between the crizotinib and chemotherapy groups in 1007, and they were overall comparable with those from 1001 and 1005, except for a smaller proportion of patients in 1007 with prior EGFR-TKI therapy (approximately 12% in 1007 versus 48% to 54% in 1001 and 1005, respectively).

As of the data cutoff date of March 30, 2012 for 1007, patients treated with crizotinib had median study treatment duration of 33 weeks (range 3–111) versus 12 weeks (range 3–90) for those in the chemotherapy arm.

The primary outcome of 1007 – improved progression-free survival - was achieved: the median progression-free survival was 7.7 months (100 events [58%]) for patients randomized to crizotinib and 3.0 months (127 events [73%]) for patients randomized to chemotherapy. The hazard ratio comparing crizotinib with chemotherapy was 0.49 (95% CI: 0.37 to 0.64). The objective response rate was also significantly better for patients randomized to crizotinib (65.3% [95% CI: 58 to 72]) as compared with chemotherapy (19.5% [95% CI: 14 to 26]) with an absolute difference of almost 46% (objective response rate ratio of 3.4 [95% CI: 2.5 to 4.7] in favour of crizotinib).

The prespecified interim overall survival analysis did not show a statistically significant benefit in favour of crizotinib. Median overall survival was estimated to be 20.3 months for crizotinib versus 22.8 months for chemotherapy (hazard ratio 1.02 [95% CI: 0.68 to 1.54]). However, 112 (64%) patients crossed over from the chemotherapy arm to crizotinib upon disease progression, thereby confounding the overall survival analysis. A post hoc analysis adjusting for crossovers suggested a trend in survival benefit with crizotinib over chemotherapy, but this was also not statistically significant.

Only a high-level description of quality of life data was available for the 1007. Crizotinib was associated with a statistically significantly greater improvement from baseline in global quality of life in patients treated with crizotinib compared with chemotherapy (estimated difference 9.84, 95% CI: 5.39–14.28). Crizotinib was also associated with a statistically significant greater improvement from baseline in symptoms and functioning (except for cognitive functioning) on the EORTC QLQ-C30/QLQ-LC13 compared with chemotherapy.

Harms outcomes in the crizotinib group of 1007 were consistent with those reported in the original pCODR systematic review. In the 1007 safety population 25 deaths occurred among patients receiving crizotinib (over half due to disease progression) compared with seven deaths among patients receiving chemotherapy. SAEs occurred in 37.2% and 23.4% of patients receiving crizotinib and chemotherapy, respectively. SAEs occurring in at least 5% of patients in the crizotinib versus chemotherapy arm included disease progression (7.6% versus 1.8%) and neutropenia (1.7% versus 8.2%).

The total AEs (all grades) observed in the crizotinib and chemotherapy arms were 100% and 98.2%, respectively, in study 1007. Notable differences between the treatment groups were higher rates of vision disorder, gastrointestinal events (diarrhea, nausea, vomiting, and constipation), elevated transaminases, edema, and dizziness among crizotinib-treated patients, whereas rash and alopecia occurred more frequently with chemotherapy. Grade 3 to 4 AEs were similar between the crizotinib and chemotherapy arms, except for elevated transaminases occurring in 15.7% of patients receiving crizotinib compared with 2.3% receiving chemotherapy. No cases of grade 3 or 4 hepatotoxicity were reported.

Updated efficacy and safety data from 1001 and 1005 were consistent with what was presented in the original pCODR systematic review.

Several key limitations of 1007 were considered. The prespecified interim analysis for overall survival (conducted at the final analysis of progression-free survival) included approximately 40% of the total number of deaths required for the final

overall survival analysis and is therefore immature. Additionally, the large percentage of patients who crossed over from chemotherapy to crizotinib makes the overall survival findings in 1007 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 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 1007 correlates with an overall survival benefit. Investigators and patients were not blinded to treatment allocation in 1007; however, response rates were assessed by independent radiology review, which might mitigate potential bias from the lack of investigator blinding.

Finally, the new and updated efficacy and safety data for crizotinib were extracted from non-peer reviewed sources (conference abstracts or presentations and clinical summaries provided by the manufacturer in the pCODR resubmission[24]), except for the published article with updated 1001 data.[1] Consequently, limitations associated with these sources of data prevent a full assessment of the quality of this evidence and caution should be exercised when drawing conclusions as to the clinical effects of crizotinib.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

There are three commonly used outcome measures in studies assessing the effects of treatments for lung cancer: overall survival, progression-free survival, and objective response rates, of which overall survival reflects direct clinical benefit to the patient and remains an optimal outcome measure. Regulatory bodies, including the U.S. FDA, allow the use of a surrogate for overall survival – such as objective response rate – as a primary outcome measure provided that it is "reasonably likely to predict clinical benefit of drugs that are intended to treat serious or life-threatening diseases".[25]

In the assessment of crizotinib for ALK-positive advanced or metastatic NSCLC, to evaluate whether the change in objective response rate could reliably predict clinical benefit (i.e., overall survival) is critically important. To date, objective response rate has been used only in a few instances as the basis for accelerated approval for advanced NSCLC, such as with pemetrexed and gefitinib, while the majority of drug approvals for NSCLC with targeted molecular therapies have been based on improvement in overall survival.[25] Nevertheless, the appropriateness of objective response rate as a surrogate in predicting a survival benefit remains inconsistent and controversial. For example, the regulatory approval of gefitinib (an inhibitor of the epidermal growth factor receptor tyrosine kinase) was initially based on improvement in objective response rate; however, subsequent studies had been unable to confirm its clinical benefit in terms of overall survival. As a result, the approval of gefitinib by the FDA for the third-line treatment of patients with locally advanced or metastatic NSCLC (after failure of both platinum-based and docetaxel chemotherapies) was withdrawn in 2011.[26] Similar to crizotinib, the

accelerated approval of gefitinib was based on single-arm, non-randomized trial data.

In 2009, Tsujino et al. reviewed 24 phase 2 trials and four phase 3 trials with a total of 6,171 patients with advanced NSCLC treated with gefitinib or erlotinib.[27] Using a linear regression analysis, the study reported a statistically significant correlation (P<0.0001) between response rate and median survival time. In addition, in a receiver operating characteristic analysis, the area under the curve predicting median survival time by response rate was 0.918. The predictive modeling analysis was inconsistent with the data obtained on overall survival in subsequent randomized controlled trials. Although it appears that response rate is strongly correlated with a survival gain, it might be more appropriate to interpret response rate in combination with a threshold effect size rather than to simply consider an arbitrary statistically significant or non-significant correlation with overall survival. As shown in a meta-analysis of randomized controlled trials for advanced NSCLC (191 trials), it appears that large differences in response rate are needed to predict a survival benefit if response rate is chosen as a surrogate primary endpoint.[23] Depending on trial sample size (with larger trials requiring smaller differences), the differences in response rate between trial treatment groups of 18% to 30% were required to reliably predict the survival benefit in advanced NSCLC trials.[23]

For Consideration with the Resubmission

The primary outcome in PROFILE 1007 was progression-free survival. As with objective response rate (as discussed above), progression-free survival is often used as a surrogate endpoint for overall survival in phase 3 oncology trials, and it is accepted by regulatory bodies, such as the U.S. FDA.[25] 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 1007, some studies have shown improvement in progression-free survival without a corresponding increase in overall survival.[13]

Li et al.[10] 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.[11] However, the review did not include the Li et al.[10] study likely because both were published in the same year (2012). Additional non-systematic reviews[12,13] 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 for identifying ALK-positive NSCLC patients who should receive targeted systemic therapy with crizotinib.[19] The Vysis assay was used to identify eligible patients for inclusion into the clinical trials for crizotinib in advanced NSCLC, PROFILE1001 and 1005.[2,4-9] 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.[28] However, the conduct of the test and interpretation of the test results require special technical training that is currently not available in routine laboratory practice throughout Canada and cost is a consideration. Hence, although ALK FISH is commercially available, without publicly disclosable information on which laboratories may be prepared to process specimen, it is not possible to confirm if the test is readily accessible to all patients with NSCLC across the jurisdictions. 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 proposed, 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.[29-32] A multicentre pan-Canadian study is ongoing to examine the appropriateness of IHC and FISH as tests to identify ALK gene rearrangements in NSCLC patients and, therefore, potential recipients of crizotinib. 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 all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that molecular testing would be required to determine the subset of patients with the ALK-positive mutation who would be candidates for crizotinib therapy and therefore, additional information on ALK testing was identified as being helpful, including the costs, accessibility and performance of the ALK test. PAG also noted that most jurisdictions have set treatment algorithms for NSCLC and additional guidance in determining how crizotinib fits into the current treatment algorithm for NSCLC would be helpful. PAG noted that crizotinib would likely be an incremental therapy, used in addition to current lines of therapy for NSCLC, and therefore, there would be additional costs to the jurisdictions. However, PAG also identified that crizotinib is an oral agent which may help to minimize costs related to chemotherapy unit and chair time.

Other

- Two phase 3 randomized clinical trials are ongoing (see Section 6.4 for further details). In brief, one trial is examining crizotinib as second-line therapy for ALK-positive patients with NSCLC versus single-agent docetaxel or pemetrexed. The randomized period of the trial has been completed and data reports are expected to be presented later in 2012. The other phase 3 trial is randomly assigning patients to first-line crizotinib or chemotherapy with pemetrexed plus a platinum agent. This trial is ongoing. The primary efficacy endpoint for both trials is progression-free survival. pCODR requested efficacy and safety data for both study 1007 and study 1014 from the manufacturer during the systematic review, but was informed the data were unavailable at the time of the request.
- **Following Resubmission:** One additional ongoing phase 3 randomized, open-label trial was identified examining the efficacy and safety of crizotinib versus cisplatin/pemetrexed or carboplatin/pemetrexed in previously untreated East Asian patients with ALK-positive NSCLC. The trial is currently recruiting patients with a minimum target of 200.
- Crizotinib is active against molecular targets besides ALK. It was initially developed as a MET inhibitor and it has activity on tumours with activated ROS, both of which are relevant molecular markers in lung cancer.[33] Therefore, crizotinib may have anti-tumour effects beyond ALK inhibition in NSCLC. The U.S. FDA requested the manufacturer to collect data on a subset of ALK-negative NSCLC patients exposed to crizotinib during study 1001.[20,21] The preliminary efficacy data for the ALK-negative cohort was updated with a cutoff date of May 27, 2011 for 23 patients. Of these patients, 19 were considered response evaluable; however, four patients were excluded from the response-evaluable group due to either lack of adequate baseline tumour assessment (n=3) or no post-baseline tumour assessment at least six weeks after the first crizotinib dose (n=1). A total of 0 complete responses and 5 partial responses were reported for an investigator assessed objective response rate of 26.3% (95% CI: 9.1% to 51.2%). Therefore, a patient with ALK-negative NSCLC whose tumour harbours over expressed or amplified MET or activated ROS could potentially respond to crizotinib based on inhibition of one of these other targets. Although these findings are suggestive of a benefit from crizotinib among ALK-negative patients, the estimate of response rate is based

on a very small cohort and is not reliable to draw conclusions. Further study on a larger cohort is required to evaluate this effect.

- One retrospective study explored whether progression-free survival with pemetrexed differed between ALK-positive and other major molecular subtypes of NSCLC, namely EGFR and KRAS mutations.[34] Among 89 eligible metastatic NSCLC patients, 19 were identified as ALK-positive (12 were EGFR-positive, 21 KRAS-positive, and 37 as negative for all three). None of the ALK-positive patients had received crizotinib before pemetrexed. Pemetrexed mono- or combination therapy was first-line therapy in 63% of ALK-positive patients and 48% among all four groups. Median progression-free survival for ALK-positive patients was 9 months (95% CI: 3 to 12 months), compared with 5.5 months (95% CI: 1 to 9 months) for EGFR mutant, 7 months (95% CI: 1.5 to 10 months) for *KRAS* mutant, and 4 months (95% CI: 3 to 5 months) for triple negative patients. In a multivariate analysis adjusting for line of therapy, mono- versus platinum and nonplatinum combination therapy, age, sex, histology, and smoking status, the only variable associated with prolonged progression-free survival on pemetrexed was ALK-positive status (hazard ratio = 0.36 [95% CI: 0.17 to 0.73], P = 0.0051).[34] This data should be considered exploratory given the very small sample size and retrospective study design.
- 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

The non randomized phase I/II (Profile 1001) and phase II trial (Profile 1005) demonstrate significant efficacy of crizotinib in achieving tumour responses in ALK-positive advanced or metastatic NSCLC. Benefits in terms of progression-free, overall survival and QoL compared to historical outcomes for the general population of advanced/metastatic NSCLC with unknown ALK mutation status are acknowledged.

The randomized phase III trial (Profile 1007) comparing crizotinib to pemetrexed or docetaxel as second-line therapy demonstrated tumour response rates consistent with what was seen in the earlier studies. Significant improvement in progression-free survival in favour of crizotinib vs cytotoxic chemotherapy was demonstrated (HR 0.49 (95% CI: 0.37-0.64)). However at this time, no overall survival benefit is evident, likely due to the expected crossover from chemotherapy to crizotinib that confounds this analysis. QoL benefits from treatment with crizotinib reflect the antitumour activity of the agent and its relatively modest toxicity profile.

Targeting a driver mutation such as ALK with crizotinib appears to be a successful treatment strategy, which is supported by the consistent tumour response rates for crizotinib reported between the three trials and the various subgroup comparisons, including gender, performance status, smoking status, and lines of prior therapy.
The tumour response rates seen with crizotinib in ALK-positive NSCLC are significantly greater than what is typically seen with existing standard systemic therapy, regardless of the line of treatment. That clinical parameters such as gender, performance status and smoking status do not predict for response to crizotinib highlights the importance of ALK companion

laboratory testing to establish ALK mutation status for the selection of the appropriate treatment population.

The safety profile of crizotinib, the spectrum and incidence of adverse effects, appears favourable in keeping with other molecularly targeted oral agents used in management of NSCLC. The frequency of adverse effects leading to discontinuation of treatment in the reported trials was low.

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

Improvement in progression-free survival and QoL is felt to be of sufficient benefit to support use of this therapy, particularly as it is associated with modest treatment-related toxicity. Thus crizotinib appears to be a superior alternative to standard single-agent chemotherapy as second-line systemic therapy in advanced/metastatic NSCLC.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC as second-line systemic therapy. Crizotinib has demonstrated a clear clinically and statistically significant benefit in terms of progression-free survival compared to standard second-line chemotherapy in one Phase III randomised study.

The Clinical Guidance Panel also acknowledges the consistency of antitumour activity of crizotinib among the trials that have been reported to date. At present, limited follow up and crossover as a potential confounding factor in the phase III trial limits the assessment of crizotinib's impact on overall survival.

With establishment of appropriate routine companion ALK mutation testing, the panel felt it is the preferred option for ALK-positive advanced/metastatic patients to have access to crizotinib as second-line systemic therapy. The results of pending trials may clarify the role of crizotinib in other lines of therapy.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Crizotinib 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.[14] It is estimated that in 2012 there will be 25,600 new cases and 20,100 deaths associated with NSCLC in Canada with an incidence and mortality rate of 54/100,000 and 42/100,000 population, respectively.[15] 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.[35] Further, the advance 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.[36]

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.[37] First-line platinum-based chemotherapy is associated with improvements in survival and quality of life.[38] 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,[39-41] 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, now have defined roles in patient treatment. 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 tumors, progression free survival (PFS) was significantly longer (HR 0.48, 95% CI 0.36-0.64, p<0.001).[42] 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).[43] A second trial (that was the first to involve a western European population), the EUROTAC trial randomized patients toa platinum based doublet (docetaxel/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).[44]

Maintenance treatment with erlotinib and pemetrexed have also shown benefit in patients after first line doublet platinum based chemotherapy, however overall patient uptake of maintenance therapy has been slow likely owing to the residual toxicity from platinum based first line doublet therapy.[45,46] The phase II SATURN trial examined erlotinib as maintenance therapy following platinum based chemotherapy met its primary endpoint of significant longer

PFS in patients treated with erlotinib (12.3 weeks) versus placebo (11.1 weeks) (HR 0.69 95%CI 0.58-0.82; p <0.0001).[47]

Randomized trials have established improved survival and quality of life from second-line chemotherapy with either docetaxel or pemetrexed.[48,49] Recent evidence has shown that the use of pemetrexed in NSCLC should be reserved for non-squamous histologies likely on the basis of elevated thymidylate synthetase levels.[45] Erlotinib has also demonstrated improved survival and symptom control in patients who progressed after one or two lines of prior chemotherapy.[50] The INTEREST Trial, a phase III, single agent, gefitinib was non-inferior versus docetaxel in second line treatment. No benefit difference was seen in those patients with EGFR gene amplification; however there was a suggestion of benefit seen in the unplanned analysis of EGFR mutant patients in terms of ORR and PFS.[51]

Third line and beyond treatment usually is based on patient overall performance status and patient motivation. Expert consensus supports that a trial of a not previously used agent is reasonable, if no formal clinical trial is available. Supportive care in all lines of therapy is appropriate and includes radiation therapy, early referral to the palliative care, psychosocial and spiritual care where appropriate.

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.[52] 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%).[2] 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).[3] 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. The precise positioning of the use of this drug in the advanced NSCLC setting remains to be defined.

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 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

As per pCODR Procedures D3.2, due to the short time frame between the original submission and the resubmission, pCODR did not seek new patient advocacy group input. The most recent patient advaocy group input received on the original pCODR submission related to Crizotinib (Xalkori) for Advanced NSCLC was provided to the Review Team to incorporate into the Clinical Guidance Report.

The following patient advocacy group provided input on the original crizotinib (Xalkori) submission for advanced non-small cell lung cancer (NSCLC) and their input is summarized below:

- Lung Cancer Canada

Lung Cancer Canada conducted a literature review of information in the public domain, and also sought input from Canadian patients on crizotinib trials (n=3), to gather information about the patient and caregiver experience with advanced non-small cell lung cancer (NSCLC) and the drug under review.

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.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with advanced non-small cell lung cancer (NSCLC)

Patient input 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. Many patients with lung cancer are diagnosed at a late stage of the disease, where treatment is not considered curative and without treatment, survival is only estimated to be 4 to 6 months. Treatment with chemotherapy may extend life expectancy to a certain extent; however, patient input reported that only approximately one quarter of this population is deemed fit enough for chemotherapy treatment.

Patients describe the symptoms of lung cancer as being severe and debilitating, with more than 90% of patients experiencing at least one severe lung cancer-related symptom and over 80% having at least three or more symptoms upon diagnosis. Some of the symptoms noted by patients included severe cough, pain, shortness of breath,

coughing up blood, weight loss, and fatigue. A majority of patients report that their symptoms interfere with their daily activities and many believe that their illness imposes significant hardships on those close to them.

Patient input indicated that 41% of Canadian patients with advanced lung cancer experienced financial hardships.

Input from the patient advocacy group indicated that patients believe that there is a stigma associated with a diagnosis of lung cancer, as smoking is the leading cause of this disease. They emphasized that lung cancer is also diagnosed in never smokers and also in patients who have previously quit smoking. Patients expressed that there appears to be little recognition that lung cancer in never smokers can be a common and deadly disease that could affect any Canadian.

4.1.2 Patients' Experiences with Current Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)

Input from the Patient Advocacy Group indicated that the standard treatment for patients with advanced NSCLC consists of intravenous chemotherapy with platinum-based doublet therapy, such as cisplatin or carboplatin combined with one of gemcitabine, vinorelbine, paclitaxel, docetaxel, or in select provinces, pemetrexed. In addition, patient input highlighted that although bevacizumab is currently approved by Health Canada for the treatment of non-squamous NSCLC in combination with paclitaxel and carboplatin, it is not currently funded by any of provinces or territories.

Patient input reported that response rates to first-line chemotherapy are approximately 20%, with up to two thirds of patients experiencing a temporary improvement in their symptoms and quality of life. However, input further indicated that responses and symptom improvement only last a few months, with a time to progression on chemotherapy of three to four months.

Patients indicated that there are significant toxicities associated with chemotherapy, including nausea, vomiting, kidney damage, nerve damage, potential hearing loss, fatigue, anorexia, and low blood counts with a risk of transfusions and neutropenic sepsis. In addition, patients may face the inconvenience of multiple blood tests, receiving intravenous therapy, and frequent hospital visits. Patient input indicated that the toxic death rate with first-line chemotherapy has been estimated at 2-5%.

Patient input reported that second-line treatment with chemotherapy is available for approximately 30% of patients. Second-line chemotherapy has an associated response rate of less than 10%, similar toxicities as those seen with first-line treatment, and modest survival gains in the order of a median of three months. It was also reported that erlotinib is recommended for all advanced NSCLC after chemotherapy failure with a survival gain in the order of two months on average and improved symptoms and quality of life. Patients indicated that erlotinib is an oral agent, which avoids the inconvenience of intravenous treatment but it is also associated with side effects, such as rash and diarrhea.

4.1.3 Impact of advanced non-small cell lung cancer (NSCLC) and Current Therapy on Caregivers

Patient advocacy group input indicated that caregivers play a key role in making decisions about the patient's treatment and care. Caregivers face the demands of providing transportation, scheduling and making hospital visits, arranging for home care, and dealing with insurers in the case of unfunded treatments, all of which can be physically and emotionally exhausting for them. Caregivers also report difficulties in juggling the competing demands of providing emotional and tangible support to patients, while meeting their ongoing obligations of home, work, and family. Input from patients also conveyed that caregivers can experience persistent psychological distress and role adjustment problems, even up to a year after patients have completed their cancer treatment. In addition, it was pointed out that the emotional demands of providing care reach their peak as lung cancer progresses.

4.2 Information about the Drug Being Reviewed

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

Input from patients without direct experience with crizotinib for advanced NSCLC indicated that patients with advanced NSCLC are seeking drug therapies that would offer any improvement in efficacy, convenience, or side effect profile over currently available therapies.

It was reported that lung cancer patients with ALK-positive disease appear to be relatively resistant to EGFR tyrosine kinase inhibitors, such as erlotinib or gefitinib, and tend to have poor outcomes when treated with chemotherapy. Therefore, patients with ALK-positive lung cancer are seeking alternative treatment options.

Input from patients indicated that based upon the results seen in clinical trials with crizotinib, they expect the benefit of crizotinib treatment to be far beyond what would be seen with chemotherapy or any other alternative therapy.

Patients with direct experience with crizotinib indicated that the most commonly experienced side effects included mild nausea and diarrhea. Other side effects that patients noted with crizotinib included visual disturbances, mild vomiting, constipation, edema, fatigue, and decreased appetite. In addition, patients noted that increases in the levels of hepatic transaminases could occur but were generally considered mild, and even when they were severe, they were not usually associated with symptoms. Input from the patient advocacy group indicated that patients considered crizotinib to have a favorable risk to benefit profile. Patients noted that crizotinib appears to have minimal side effects. Additionally, they considered the side effects to be manageable based upon crizotinib studies and to be less toxic than chemotherapy.

As crizotinib is orally administered, patients commented that they are able to take the medication at home, thus avoiding having to use needles and make trips to the hospital. In addition, with an oral medication, both patients and their caregivers reported being able to save time off of work and being able to live a more active life.

Patients expressed that crizotinib represents a major advance for ALK-positive lung cancer patients and has revolutionized their treatment and dramatically improved outcomes, which is considered important in this group of patients who would have otherwise had a grim prognosis. Patients report that many of them are able to be active and high-functioning, and are living longer than two years on treatment. Furthermore, crizotinib provides hope for patients in improving their long-term health and well-being. Input indicated that crizotinib is truly life altering for patients and their families, giving many a new lease on life, even if it only for a few years.

4.3 Additional Information

Lung Cancer Canada 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.

Lung Cancer Canada also indicated that screening patients for the ALK mutation presents as a challenge, as there is currently a lack of infrastructure for testing key biomarkers, such as EGFR, in newly diagnosed advanced NSCLC across Canada. The patient advocacy group stressed that the molecular profile of lung cancers is critically important in determining how to best treat these patients and optimize their outcomes.

Lung Cancer Canada suggested that they would support a national ALK testing strategy, such as pre-screening with immunohistochemistry (IHC) as it is an inexpensive and readily available test, to help determine the small number of cases that would need to undergo additional testing with fluorescence in situ hybridization (FISH).

The patient advocacy group also pointed out that crizotinib is an oral therapy, and therefore, the funding of this agent could be variable across the country. They emphasized their belief that all Canadians should have access to important treatments, such as crizotinib, and also the importance of ensuring provincial funding for crizotinib in the small number of patients who would be eligible for this therapy. The patient group considered that this was particularly important given than ALK-positive lung cancer is more commonly seen in younger patients and patients with lung cancer may experience financial hardships.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for crizotinib (Xalkori) for the treatment of advanced non-small cell lung cancer (NSCLC). 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.pcodr.ca).

Overall Summary

Input on the original crizotinib (Xalkori) review was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. The PAG input from the original crizotinib submission was reviewed by PAG members and due to the short time frame between the original submission and the resubmission, PAG members had confirmed the original PAG input as sufficient for the resubmission. From a PAG perspective, it was noted that molecular testing would be required to determine the subset of patients with the ALK-positive mutation who would be candidates for crizotinib therapy and therefore, additional information on ALK testing was identified as being helpful, including the costs, accessibility and performance of the ALK test. PAG also noted that most jurisdictions have set treatment algorithms for NSCLC and additional guidance in determining how crizotinib fits into the current treatment algorithm for NSCLC would be helpful. PAG noted that crizotinib would likely be an incremental therapy, used in addition to current lines of therapy for NSCLC, and therefore, there would be additional costs to the jurisdictions. However, PAG also identified that crizotinib is an oral agent which may help to minimize costs related to chemotherapy unit and chair time.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG noted that there is a potential for crizotinib to be used in different NSCLC settings and therefore, there could be many different comparators, depending upon which setting it is being used in. However, PAG also noted that the current therapies available for NSCLC have not been specifically evaluated in the subset of patients who are ALK-positive, so it may be hard to identify a 'true' comparator.

Erlotinib was identified by PAG as being a potential comparator to crizotinib. PAG noted that erlotinib is administered once daily whereas crizotinib is administered twice daily and there could potentially be adherence issues in certain patients having to use a twice daily administration schedule.

PAG also recognized that many of the agents used to treat NSCLC are administered as IV and require chemotherapy unit resources. As crizotinib is an oral therapy, if it were used in place of IV administered chemotherapy, there could potentially be cost savings which would need to be factored into the economic analysis.

PAG noted that some jurisdictions have had difficulty implementing funding decisions for other NSCLC medications, as they required molecular testing which jurisdictions could not access or implement, such as the EGFR testing required for gefitinib. PAG recognized that this could be a similar situation for crizotinib, as molecular testing is required to find the appropriate patient subset for crizotinib.

PAG recognized that it is highly likely that crizotinib would be an incremental therapy, used in addition to current lines of therapy for NSCLC, and therefore, there would be additional costs to the jurisdictions, which could be a barrier to implementing a funding decision for crizotinib.

PAG noted that the data to support the submission of crizotinib to Health Canada was based upon two single-arm studies, a Phase I study and a Phase II study. PAG noted that the strength of clinical data available for some other agents used in the treatment of advanced NSCLC appears to be stronger than the data available for crizotinib. Based on the level of available clinical evidence for crizotinib, PAG recognized that there is a possibility that crizotinib may receive a Notice of Compliance with Conditions (NOC/c) from Health Canada. In this case, PAG noted that it would be central for the jurisdictions to know the reasons behind the Health Canada and/or FDA approval and the strength of clinical and safety data, as it was noted that a previous cancer drug granted an NOC/c from Health Canada recently had its authorization withdrawn.

5.2 Factors Related to Patient Population

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.

Based upon the currently available evidence for crizotinib, it would likely be used in ALK-positive patients who have failed standard treatments for advanced NSCLC. However, PAG noted that there may potentially be physicians or patients wanting to use crizotinib as a first-line therapy for ALK-positive advanced NSCLC. There are currently ongoing trials comparing crizotinib to first- and second-line chemotherapies.

Some jurisdictions noted that indication creep would not likely be an issue with crizotinib, especially for those provinces who have a mechanism in place for review of patient-specific requests. However, other jurisdictions noted that there was the potential for indication creep with crizotinib into the adjuvant setting of NSCLC or potentially for those patients who have tested ALK negative.

5.3 Factors Related to Accessibility

PAG noted that crizotinib is an oral medication, which would make it more accessible for patients and be an enabler for this therapy. In addition, crizotinib is given as monotherapy and therefore, no other agents are given concomitantly, which would also be an enabler to accessibility. On the other hand, in some jurisdictions, oral therapies are funded under provincial drug plans and not all provincial drug plans cover the entire patient population, which may be a barrier to access as these patients would have to pay 'out of pocket' for the medication if they did not have private insurance.

PAG recognized that molecular testing would be required to determine the subset of patients with the ALK-positive mutation who would be candidates for crizotinib therapy, which could potentially be a barrier to a funding implementation for crizotinib. PAG noted that the requirement for molecular testing would add additional costs to treatment and as it is a companion diagnostic, funding of the test itself could be a separate consideration from the funding of crizotinib. Some jurisdictions do not have molecular testing available in their province and other options, such as sending tissue samples out of province, would need to be explored. Furthermore, it was noted that some jurisdictions have had difficulties implementing funding decisions for other NSCLC treatments in the past as they did not have access to the appropriate molecular testing required. PAG identified that additional information on ALK testing would be helpful, including the costs, accessibility and performance of the test.

As crizotinib could be used as a sequential therapy after other NSCLC treatments, PAG noted that the additional costs of this medication would be barrier in implementing a funding decision.

5.4 Factors Related to Dosing

As crizotinib is an oral therapy, PAG noted that it could be self-administered by patients in less central areas with appropriate monitoring by an oncology health team, which would be an enabler for implementing a funding decision for crizotinib.

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 and potentially be a risk for medication errors. In addition, PAG would appreciate if there is any data to support the effectiveness of the decreased dosing regimens.

PAG identified that crizotinib is administered twice daily, whereas erlotinib, a possible comparator to crizotinib, is administered once daily and there could potentially be adherence issues in certain patients having to use a twice daily administration schedule.

5.5 Factors Related to Implementation Costs

As mentioned above, PAG identified that molecular testing would be required to identify the subset of patients who have the ALK mutation and would therefore be eligible for crizotinib therapy. PAG noted that this test would add costs to the implementation of crizotinib treatment and population-level implementation of this test may be problematic for a number of reasons in certain jurisdictions, which could be a barrier. It should also be factored into the economic analysis.

PAG noted that most jurisdictions have set treatment algorithms for NSCLC and there may be some difficulties with determining how crizotinib fits into the current treatment algorithm for NSCLC. One jurisdiction identified that there may be requests for pemetrexed as a second-line therapy, in combination with platinum doublet therapy, as there are reports that ALK-positive patients respond better to pemetrexed.

As crizotinib is administered orally, PAG identified that there could potentially be savings with crizotinib as chemotherapy units and chair time would not be utilized. However, it was also noted that toxicity monitoring would still be required with crizotinib and would require clinic resources. In particular, crizotinib can cause visual abnormalities which would require assessment and monitoring by ophthalmologists.

As crizotinib could be used as a sequential therapy after other NSCLC treatments, PAG noted that there would be additional costs as patients would be receiving an extra line of therapy for NSCLC.

5.6 Other Factors

No other factors that could affect the feasibility of implementing a funding recommendation were identified.

6 SYSTEMATIC REVIEW

Upon review, one change was made to the original systematic review protocol: the trial design criteria were modified to exclude case series and case reports. No other modifications were necessary.

6.1 Objectives

To evaluate the effect of crizotinib on patient outcomes compared with standard therapies or placebo in the treatment of 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 of ALK mutation testing in advanced or metastatic non-small cell 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 non-RCTs (excluding case series and case reports)	Patients with ALK-positive advanced NSCLC Subgroups: • Previous treatment vs. treatment naive • Histologic type • ECOG PS (0—1 vs. ≥2) • Sex • Smoking status • EGFR mutation status	Crizotinib at recommended dose 250 mg orally twice daily	**Active** Cytotoxic Chemotherapies: • Platinum-doublet • Pemetrexed • Docetaxel • Gemcitabine • Vinorelbine Anti-EGFR-TK: • Erlotinib • Gefitinib **Non-active** • Placebo	• Overall survival • Progression-free survival • **QoL** • Objective response rate • **SAEs** • **AEs** • WDAEs

Abs=antibodies; **AE**=adverse events; **ALK**=anaplastic lymphoma kinase; **CR**=complete response; **ECOG PS**=Eastern Cooperative Oncology Group Performance Status Scale; **EGFR**=epidermal growth factor receptor; **PR**=partial response; **QoL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **TK**=tyrosine kinase; **VEGF**=vascular endothelial growth factor; **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).

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 (2012, Issue 12) via Wiley; 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 crizotinib and Xalkori.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The search is considered up to date as of January 6, 2013.

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 Ontario Institute for Cancer Research – Ontario 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:

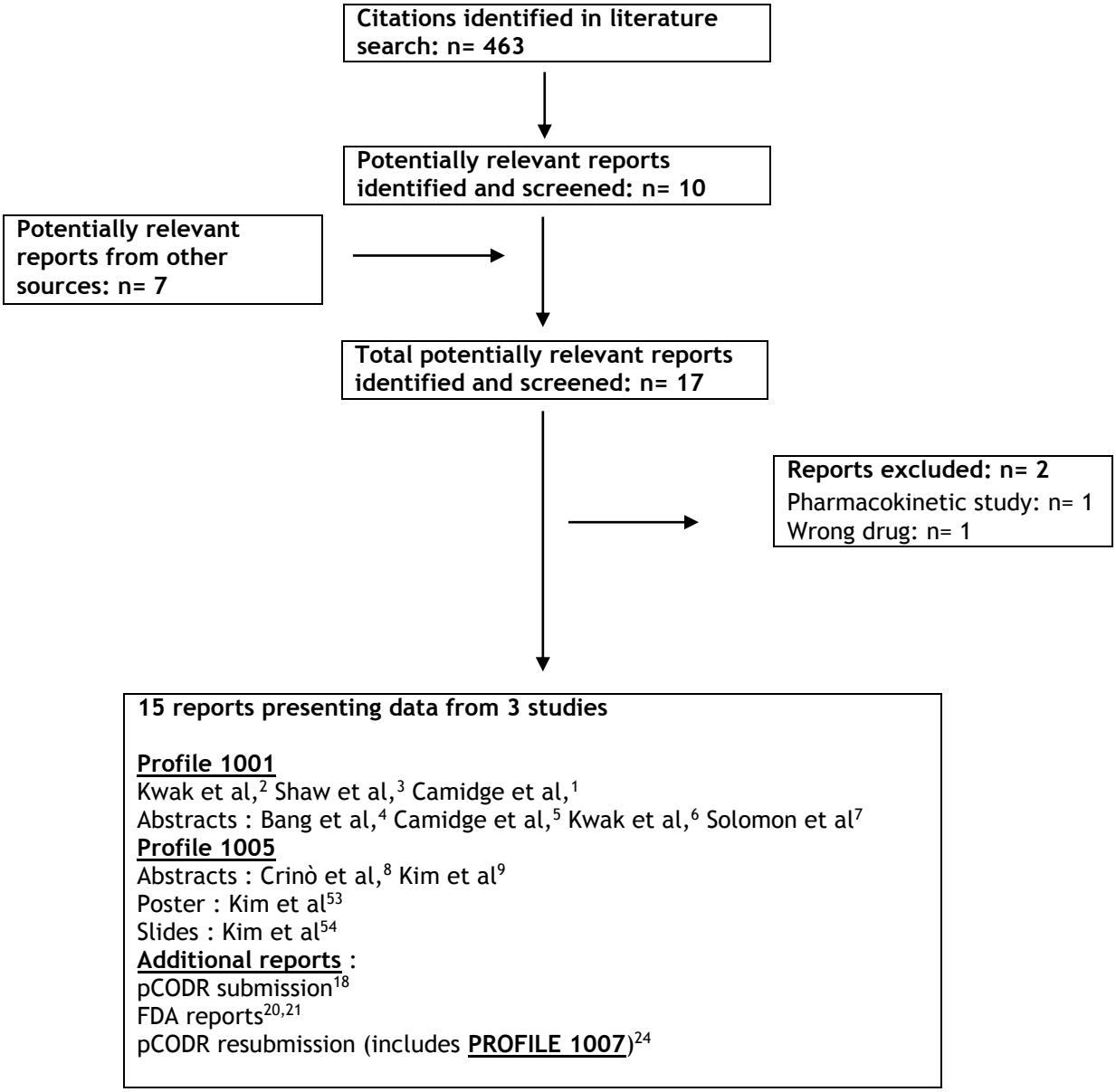
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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, 15 reports were included in the pCODR systematic review[1-9,18,20,21,24,53,54] and 2 reports were excluded. Studies were excluded because they were the wrong study design (pharmacokinetic study)[55] or the wrong drug was studied (crizotinib was not the investigational drug).[34]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

Two clinical trials met the inclusion criteria for this systematic review. The first, PROFILE1005 (hereinafter referred to as 1005) was a multicentre, multinational, phase 2, open-label, single-arm study of the efficacy and safety of crizotinib in patients with advanced (locally advanced or metastatic) non-small cell lung cancer (NSCLC) with genetic rearrangements involving the anaplastic lymphoma kinase (ALK) gene locus.[8,9,53,54] The second, PROFILE1001 (hereinafter referred to as 1001) was a multicentre, multinational, phase 1, open-label, dose-escalation, safety, pharmacokinetic, pharmacodynamic, and antitumor activity study of crizotinib administered orally to patients with advanced malignancies.[2,4-7] A summary of the trials is presented in Table 2.

Given the paucity of published literature for these studies, information on the design, conduct, analysis, and the extracted data come primarily from the U.S. Food and Drug Administration (FDA) medical and statistical reviews of crizotinib for advanced non-small cell lung cancer (NSCLC).[20,21] Data on overall survival were also extracted from a published retrospective analysis of a cohort drawn from study 1001.[3]

Of note, updated efficacy and safety data, in the form of a conference abstract and presentation from the 2012 ASCO Annual Meeting,[53,54] were provided by the manufacturer when the systematic review was near completion. The new information was evaluated and the pCODR Lung Clinical Guidance Panel considered that it would not alter the clinical interpretation of the data for crizotinib in advanced NSCLC, therefore, data were not extracted and included in this report.

Included Studies for the Resubmission

The manufacturer submitted five reports presenting new data from three studies: updated results from 1001 (Camidge et al.[1], also identified in the pCODR literature search) and 1005 (2 conference abstracts[24]); and data from PROFILE1007 (conference abstract and top-line summary report[24]), an open-label, multicentre, randomized, phase 3 trial of crizotinib versus second-line standard of care chemotherapy, pemetrexed or docetaxel, in ALK-positive, advanced NSCLC patients who received one prior chemotherapy regimen that was platinum-based. No additional studies were identified by the pCODR literature search.

A summary of 1007 has been added to Table 2.

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of the Included Studies*[2-9,24]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
PROFILE1005 (Study A8081005)[8,9] January 7, 2010 — Ongoing Phase 2 MC, MN, OL, SA safety and efficacy for ALK-positive advanced NSCLC n = 250 planned n = 148 enrolled n = 136 treated Funded by manufacturer, Pfizer	• Locally advanced/metastatic NSCLC** • ALK mutation† (ALK break-apart FISH assay) • Prior treatment for advanced NSCLC • 1 of the following criteria: o Randomized to pemetrexed or docetaxel groups of Phase 3 Study A8081007 and discontinued from treatment due to disease progression o Ineligibility for Study A8081007 due to receiving prior chemotherapy • ECOG-PS ≤3 • Adequate organ function	Crizotinib 250 mg orally BID in 21-day cycles	*Primary* • Adverse events • Objective response rate (RECIST v. 1.1) *Secondary* • Duration of response • Time to response • Disease control rate • Overall survival • Progression-free survival

Table 2: Summary of Trial Characteristics of the Included Studies (cont'd)*[2-9,24]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
PROFILE1001 (Study A8081001)[2,4-7] December 26, 2006 — Ongoing 2-part Phase 1/2 MC, MN, OL, SA, DE, PK, PD, safety, efficacy trial **Dose Escalation Cohort** n = 40 planned n = 37 enrolled n = 37 treated **ALK-positive NSCLC Recommended Phase 2 Dose Cohort** n = 25 planned n = 174 enrolled n = 119 treated Funded by Pfizer **Survival Cohort** (Shaw et al.)[3] Retrospective analysis with 2 historical control groups n = 82 ALK-positive, crizotinib-treated n = 36 ALK-positive, crizotinib-naïve controls n = 320 ALK-negative controls Investigator initiated	**All PROFILE1001 Cohorts** • Measurable disease (solid tumours) per RECIST v. 1.0 • Able to receive ≥2 treatment cycles • Adequate organ function **Dose Escalation Cohort** • Advanced malignancies** (not leukemias) refractory to standard therapy/no standard of care therapy available • ECOG-PS ≤1 **Recommended Phase 2 Dose Cohort** • Advanced malignancies** meeting 1 of the following criteria: o ALK-positive mutation† o c-Met amplification and/or c-Met kinase domain activating mutations o Mutations leading to altered transcriptional regulation of c-Met and/or HGF o ROS gene mutations • ECOG-PS ≤2 **Survival Cohort** • One of first 82 patients enrolled in PROFILE1001 through February 10, 2010 • Historical control groups o ALK-positive NSCLC, crizotinib-naïve patients identified retrospectively (1998 to 2008) or prospectively (screened for PROFILE1001 through February 10, 2010) o ALK-negative (screened for PROFILE1001 through February 10, 2010); includes EGFR-positive and wild-type patients	**Dose Escalation Cohort‡** Crizotinib orally in continuous 28-day cycles doses increased 50 mg QD to 300 mg BID • No concurrent anticancer agents • Hematopoietic growth factors after treatment Cycle 1 • Medications for supportive care (antiemetics, analgesics, etc.) allowed **Recommended Phase 2 Dose Cohort** Crizotinib 250 mg orally BID in 21-day cycles **Survival Cohort** ALK-positive, crizotinib-treated: • crizotinib 250 mg orally BID in 21-day cycles (PROFILE1001 protocol) Controls: • Never received crizotinib • Any other advanced NSCLC systemic therapy	**Dose Escalation Cohort** Adverse events MTD/DLT PK/PD profile **Recommended Phase 2 Dose Cohort** *Primary* • Adverse events • Objective response rate (RECIST v. 1.0) *Secondary* • Duration of response • Time to response • Disease control rate • Overall survival • Progression-free survival **Survival Cohort** Overall survival

Table 2: Summary of Trial Characteristics of the Included Studies (cont'd)*[2-9,24]			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
New Studies identified for the Resubmission			
PROFILE1007 (A8081007)[24] February 5, 2010 — February 23, 2012 Data cutoff: March 30, 2012 Phase 3, MC, MN, OL, RCT n = 318 planned n = 347 enrolled n = 343 treated Funded by manufacturer, Pfizer	• Locally advanced/metastatic NSCLC** • ALK mutation† (ALK break-apart FISH assay) • 1 prior treatment (platinum-based chemotherapy) 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) • Prior EGFR-TKI (yes/no)	*Intervention* Crizotinib 250 mg orally BID in 21-day cycles (n=173; n=1 randomized did not receive crizotinib) *Comparator* Pemetrexed 500 mg/m^2 Or Docetaxel 75 mg/m^2 intravenously, day 1, 21-day cycles (n=174; n=3 randomized did not receive chemotherapy)	*Primary* • Progression-free survival (RECIST v. 1.1) *Secondary* • Objective response rate (RECIST v. 1.1) • Duration of response • Disease control rate • Overall survival • Adverse events • Patient-reported outcomes

ALK = anaplastic lymphoma kinase; **BID** = twice daily; **DE** = dose-escalation; **DLT** = dose limiting toxicity; **ECOG-PS** = Eastern Cooperation Oncology Group performance status; **EGFR-TKI** = epidermal growth factor receptor tyrosine kinase inhibitor; **EML4** = echinoderm microtubule-associated protein-like 4; **FISH** = fluorescence in-situ hybridization; **MC** = multicentre; **MN** = multinational; **MTD** = maximum tolerated dose; **NR** = not reported; **NSCLC** = non-small cell lung cancer; **OL** = open-label; **PD** = pharmacodynamics; **PK** = pharmacokinetic; **QD** = once daily; **RCT** = randomized controlled trial; **RECIST** = Response Evaluation Criteria in Solid Tumors; **SA** = single-arm

Note: For the original pCODR submission, updated efficacy and safety data for Profile 1005 were presented at the 2012 ASCO Annual Meeting[53,54] with a data cutoff date of January 2, 2012 (mature population: n = 261). These data were included in the **resubmission** (presented at 2012 ESMO Annual Meeting[24]) along with additional 1005 patient-reported outcomes (also presented ESMO). Updated efficacy and safety data for Profile 1001 for the resubmission were published by Camidge et al.[1] and submitted by the manufacturer and identified in the pCODR literature search.

* Study descriptions from the published reports, abstracts and FDA medical and statistical reports[20,21]

** Histologically or cytologically proven.

† Translocation or inversion (e.g., resulting in EML4-ALK fusion), defined by increase in distance of 5' and 3' ALK probes or the loss of the 5' probe.

‡ Dose escalation occurred in 100% increments until either of the following happened: (1) drug related toxicity of Grade 2 severity occurs in ≥2 patients within a dose level; or (2) mean unbound area under the curve $(AUC)_{0\text{-}24}$ exceeds the highest unbound AUC tested in the 1-month toxicology studies. Escalation increments then occurred at 40%.

a) Trials

Study 1005

Study 1005[8,9,20,21] was a phase 2 study examining the safety and efficacy of crizotinib among patients with a histologically or cytologically proven diagnosis of (locally advanced or metastatic) NSCLC that was positive for translocation or inversion events involving the ALK gene locus. Patients with the ALK mutation were identified using the companion diagnostic test, the Vysis ALK break apart fluorescence in situ hybridization (FISH) assay performed at a central laboratory (Abbott Molecular, Des Plaines, IL, U.S.; see section 7 for a description of the test).

Patients were also eligible for inclusion if they: (1) were randomized into the chemotherapy group (pemetrexed or docetaxel) of the ongoing phase 3 second-line therapy study A8081007 and progressed on treatment; (2) had received prior chemotherapy and were ineligible for study A8081007; (3) had Eastern Cooperative Oncology Group (ECOG) performance status ≤3; or (4) had adequate organ function.

Enrollment of study 1005 was ongoing as of the study cutoff date (15 September 2010) and 148 patients had been enrolled from 66 study sites in North America, Europe, Asia, and Australia. A total of 136 patients had received at least one dose of crizotinib. The sample size of 250 patients was determined based on the expected number of patients who would cross-over from the chemotherapy comparator group of the phase 3 study, A8081007 (n = 100), and additional patients who would be enrolled based on other eligibility criteria (n = 150). According to the FDA statistical review, this sample size was adequate to detect adverse events of low frequency (≥1%).[21]

The primary efficacy endpoint was the objective response rate (complete response plus partial response) and was based on the response-evaluable population. Efficacy analyses were based on the investigator's evaluation of disease assessments. Study treatment continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol non-compliance. Crizotinib treatment could be continued after disease progression if the patient appeared to receive clinical benefit as judged by the investigator. Radiographic disease assessments for objective response and progression were performed at 6-week intervals (12-week intervals for bone scans) following the first dose of crizotinib. All available tumor assessments were also reviewed by independent reviewers and are also reported. A computed tomography or magnetic resonance imaging scan was performed whenever disease progression was suspected (e.g., symptomatic deterioration). The determination of antitumor efficacy was based on objective tumor assessments according to RECIST version 1.1.

The secondary efficacy endpoints included duration of response, time to tumor response, disease control rate, progression-free survival, and overall survival.

No statistical comparisons were conducted.

Study 1001

Study 1001[2,4-7,20,21] was a two-part phase 1/2 trial. It was originally designed as a phase 1 dose-escalation study in patients with any tumor type (except leukemia) to evaluate the safety and pharmacokinetics of the maximum tolerated dose of crizotinib. However, following evidence of "dramatic improvement in symptoms"[2] (stable disease at 1.5 and 7 months)[20] among two patients with ALK-positive NSCLC treated in the 50 mg daily cohort, and in consultation with the U.S. FDA, the manufacturer expanded the cohort (recommended phase 2 dose cohort) enrolling patients with ALK-positive NSCLC was established. The maximum tolerated dose was determined to be 250 mg given orally twice daily.

In addition to the ALK-positive NSCLC recommended phase 2 dose cohort, patients were also enrolled into a recommended phase 2 dose ALK-negative NSCLC cohort (n = 5), and in the recommended phase 2 dose other cohort (n = 50), from 8 sites in the United States, Korea, and Australia.[20]

The recommended phase 2 dose ALK-positive NSCLC cohort will be the focus for this systematic review of study 1001.

The recommended phase 2 dose cohort study was a multicenter, multinational, open-label, safety and efficacy study of crizotinib. The key inclusion criteria were:

- Histologically confirmed advanced malignancies that meet one of the following criteria:
    - ALK-positive translocations or gene amplification including but not limited to NPM-ALK-positive anaplastic large cell lymphoma, inflammatory myofibroblastic tumors or echinoderm microtubule-associated protein-like 4 (EML4)-ALK-positive non-small cell lung cancer
    - Positive for c-Met amplification by FISH (excluding polysomy) or positive for known c-Met kinase domain activating mutations
    - Chromosomal translocations/fusions that lead to altered transcriptional regulation of c-Met and/or HGF
    - Positive for chromosomal translocations at ROS gene.
- Measurable solid tumours as per RECIST version 1.0
- ECOG performance status ≤2

As of the clinical data cutoff date (September 15, 2010), Study 1001 treated 119 patients in the recommended phase 2 dose ALK-positive cohort. The recommended phase 2 dose ALK-positive NSCLC cohort in Study 1001 was originally designed to enroll at least 25 patients. During the study, enrollment was expanded to further explore the safety and efficacy of this cohort. There was no pre-specified sample size.[21]

The primary efficacy endpoint was objective response rate (complete plus partial response) according to RECIST v1.0. Assessment of objective response rate used the investigator's recorded measurements and assessments for target, non-target, and new lesions. In addition, all available scans were retrospectively reviewed by independent review.

The secondary efficacy endpoints included duration of response, time to tumor response, disease control rate, progression-free survival, and overall survival.

In Study 1001, ALK-positive NSCLC was identified using a number of local clinical trial assays.

An independent retrospective survival analysis of the first 82 patients (enrolled through February 10, 2010) treated in the recommended phase 2 dose ALK-positive cohort of study 1001 was also conducted.[3] The analysis examined overall survival in patients with ALK-positive advanced NSCLC treated with crizotinib, compared with 36 ALK-positive patients from trial sites who were not given crizotinib (ALK-positive controls), 67 patients without ALK rearrangement but positive for EGFR mutation, and 253 wild-type patients lacking either ALK rearrangement or EGFR mutation. Differences in overall survival were assessed using subsets of clinically comparable ALK-positive and ALK-negative patients.

New Data: Study 1007

Study 1007[24] was a phase 3 randomized controlled trial of crizotinib (n=174) versus second-line standard of care chemotherapy (n=174), pemetrexed or docetaxel, in ALK-positive, advanced NSCLC patients who received only one prior (platinum-based) chemotherapy regimen. Patients were also included if they had an ECOG performance status of ≤2. As well, those with treated brain metastases were eligible for inclusion.

Patients were randomized 1:1 to crizotinib or chemotherapy, stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). A centralized random permuted block design was used to balance the treatment assignments within the strata. The first choice for patients randomized to chemotherapy was pemetrexed unless patients received pemetrexed as part of their prior therapy or had squamous histology.

The primary outcome of 1007 was progression-free survival. Patients continued on treatment until RECIST (v1.1)-defined progressive disease as determined by Independent Radiology Review, unacceptable toxicity, consent withdrawal, or death. Patients could continue treatment beyond the point of disease progression at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit. Patients treated with chemotherapy who had disease progression had the option to switch treatment and receive crizotinib in a separate trial (study 1005).

Key secondary outcomes of 1007 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 chemotherapy.

The final analysis for progression-free survival was specified to be conducted after 217 events of disease progression or deaths due to any cause were observed; no interim analyses based on progression-free survival were planned for 1007. However, one prespecified interim analysis for overall survival, at the time of final progression-free survival analysis, was performed. The final overall survival analysis is planned to be conducted when 241 deaths occur. The sample sizes were based on detecting a hazard ratio of 0.64 (or increase in median progression-free survival from 4.5 to 7 months) to achieve 90% power for the primary outcome, progression-free survival, and on detecting a 44% increase in overall survival with 80% power.

A step-down procedure was applied to the efficacy endpoints in order to control family-wise Type I error for the comparison between crizotinib and chemotherapy,

in the following order: progression-free survival, objective response rate, and overall survival. Progression-free survival and objective response rate were tested at the 1-sided 0.025 level (2-sided 0.05 level), while overall survival was tested at the 1-sided 0.0004 level corresponding to the number of overall survival events observed at the final progression-free survival analysis.

b) Populations

Median age was 52 years on 1005 and 51 years on 1001 (Table 3).[20,21] The female/male ratio was similar on both studies with 47% and 50% male, respectively. The majority of the patients from both studies had an ECOG performance status of ≤1, were non-smokers or former smokers, and had a diagnosis of adenocarcinoma. Only 15 patients in study 1001 had no prior systemic treatments and, thus, received crizotinib as first-line treatment.

Table 3: Baseline Patient Characteristics[20,21]

	PROFILE1005 N = 136	PROFILE1001 N = 119
Male, n (%)	64 (47.1)	59 (49.6)
Age, median years [range]	52 [29 to 82]	51 [21 to 79]
ECOG performance status, n (%)		
0	37 (27.2)	41 (34.5)
1	74 (54.4)	63 (52.9)
2	25 (18.4)	14 (11.8)
3	0	1 (0.8)
Smoking status, n (%)		
Never smoked	92 (67.6)	86 (72.3)
Former smoker	39 (28.7)	32 (26.9)
Current smoker	5 (3.7)	1 (0.8)
Stages, n (%)		
Locally advanced	9 (6.6)	5 (4.2)
Metastatic	127 (93.4)	114 (95.8)
Histologic subtype, n (%)		
Adenocarcinoma	130 (95.6)	116 (97.5)
Squamous cell carcinoma	0	1 (0.8)
Adenosquamous carcinoma	3 (2.2)	0
NSCLC NOS	2 (1.5)	1 (0.8)
Prior therapy, n (%)		
Surgery	135 (99.3)	117 (98.3)
Radiation therapy	77 (56.6)	68 (57.1)
Chemotherapy	136 (100.0)	103 (86.6)
Number of prior chemotherapy regimens for advanced/metastatic disease, n (%)		
0	0	15 (12.6)
1	16 (11.8)	37 (31.1)
2	41 (30.1)	24 (20.2)
3	39 (28.7)	17 (14.3)
≥4	40 (29.4)	26 (21.8)
Prior systemic therapy, n (%)		
Platinum-based	129 (94.9)	105 (88.2)
EGFR-TKI	74 (54.4)	57 (47.9)

ECOG = Eastern Cooperative Oncology Group; **EGFR-TKI** = epidermal growth factor receptor tyrosine kinase

Table 3: Baseline Patient Characteristics[20,21]		
	PROFILE1005 N = 136	PROFILE1001 N = 119
inhibitor; **NSCLC** = non-small cell lung cancer		

The retrospective survival analysis by Shaw et al.[3] was conducted on the first 82 patients treated in study 1001 and, therefore, the characteristics of the ALK-positive/crizotinib-treated group reflects those presented in Table 3. For the primary comparison, between ALK-positive/crizotinib-treated and ALK-positive/crizotinib naïve (control) patients, both groups were well-balanced in terms of demographic features, including age, sex, ethnic origin, and smoking history (Table 4). The authors did not compare performance status since it was not consistently assessed in control patients at the start of each line of therapy. Patients who received crizotinib had a greater range in number of previous therapies than controls (0-7 versus 1-4), which could have contributed to their survival advantage. However, the median number of prior therapies was 2 in both groups. Exposure to platinum-based chemotherapy was similar between the two groups, as was exposure to pemetrexed and erlotinib.

Table 4: Summary of Characteristics of ALK-positive Patients from Shaw et al. Retrospective Survival Analysis[3]		
	ALK-positive, Crizotinib-treated, non-Korean* (n = 56)	ALK-positive Controls (n = 36)
Age, median years [range]	51 [28 to 78]	51 [32 to 78]
Sex, n (%)		
Male	30 (54)	16 (44)
Female	26 (46)	20 (56)
Smoking history, n (%)		
Never	46 (82)	24 (67)
≤10 pack years	7 (13)	7 (19)
>10 pack years	3 (5)	5 (14)
Histologic subtype, n (%)		
Adenocarcinoma	54 (96)	34 (94)
Squamous cell carcinoma	1 (2)	1 (3)
Large-cell	1 (2)	1 (3)
Brain metastases, n (%)		
No	27 (48)	19 (53)
Yes	29 (52)	17 (47)
Previous lines of treatment, median [range]	2 [0 to 7]	2 [1 to 4]
Previous platinum regimen, n (%)		
No	12 (21)	6 (17)
Yes	44 (79)	30 (83)
Previous pemetrexed†, n (%)		
No	26 (46)	12 (33)
Yes	30 (54)	24 (67)
Previous erlotinib‡, n (%)		
No	29 (52)	20 (56)
Yes	27 (48)	16 (44)

* 82 ALK-positive/crizotinib patients were included. No ALK-positive controls were identified at the Korean study site by the cutoff date of Feb 10, 2010, and since Asians might have different crizotinib pharmacokinetics than white people Shaw et al. compared control, crizotinib-naïve patients with the non-Korean cohort of crizotinib-treated patients
† Includes pemetrexed or any pemetrexed-based regimen
‡ Includes erlotinib or any erlotinib-based regimen

New Data: 1001 and 1005

As of the updated cutoff date of June 1, 2011, an additional 30 patients were evaluable in study 1001 (total N=149). Overall patient characteristics remained the same as those reported in the original submission, although there was a small increase in the number of patients not previously treated for advanced NSCLC (n=24 [16%]).[1]

A total of 901 ALK-positive patients evaluated as of the updated data cutoff date of January 2, 2012 for study 1005, 261 were evaluable, amounting to an additional 125 patients from the original submission. There were no important differences in patient characteristics between the two follow-up periods for 1005, except the updated population included 3 patients (1.1%) with an ECOG performance status of 3.

New Data: 1007

Key demographic and baseline characteristics for patients in 1007 were balanced between the crizotinib and chemotherapy groups as shown in Table 5. Baseline patient characteristics in 1007 were comparable with those from 1001 and 1005, except for a smaller proportion of patients in 1007 with prior EGFR-TKI therapy.

Table 5: Baseline Patient Characteristics for PROFILE 1007, FAS[24]		
	Crizotinib (n=173)	Chemotherapy (n=174)
Male, n (%)	75 (43.3)	78 (44.8)
Age, median years [range]	51 [22 to 81]	49 [24 to 85]
ECOG performance status, n (%)		
0	72 (41.6)	65 (37.4)
1	84 (48.6)	95 (54.6)
2	16 (9.2)	14 (8.0)
Smoking status*, n (%)		
Never smoked	108 (62.4)	111 (63.8)
Former smoker	59 (34.1)	54 (31.0)
Current smoker	5 (2.9)	9 (5.2)
Stages, n (%)		
Locally advanced	7 (4.0)	16 (9.2)
Metastatic	165 (95.4)	158 (90.8)
Histologic subtype, n (%)		
Adenocarcinoma	163 (94.2)	160 (92.0)
Squamous cell carcinoma	0	3 (1.7)
Large cell carcinoma	1 (<1.0)	1 (<1.0)
Adenosquamous carcinoma	4 (2.3)	3 (1.7)
Other	4 (2.3)	7 (4.0)
Brain metastases, n (%)		
Present	60 (34.7)	60 (34.5)
Absent	113 (65.3)	114 (65.5)
EGFR-TKI positive, n (%)		
Yes	20 (11.6)	21 (12.1)
No	153 (88.4)	153 (87.9)

ECOG = Eastern Cooperative Oncology Group; **EGFR-TKI** = epidermal growth factor receptor tyrosine kinase inhibitor; **FAS**=full analysis set; **NSCLC** = non-small cell lung cancer

* Not reported for 1 patient in the crizotinib group

c) Interventions

Patients in 1005 and the recommended phase 2 dose ALK-positive cohort of study 1001 received the recommended dose of crizotinib 250 mg twice daily, administered orally continuously in 21-day cycles.[20] Cycles were defined in 21-day treatment periods to facilitate scheduling of visits and assessments.

New Data: 1007

Patients were randomized to receive oral daily crizotinib at a starting dose of 250 mg BID, or intravenous pemetrexed 500 mg/m^2 on Day 1 of every cycle or docetaxel 75 mg/m^2 on Day 1 of every cycle. Treatments were administered in 3-week cycles.

d) Patient Disposition

Both studies are ongoing and contain several populations with a variety of cutoff dates. The pre-planned data cutoff date for both studies was September 15, 2010, and a 60-day data update was submitted to the U.S. FDA (and Health Canada) with a cutoff date of February 1, 2011. The table below outlines these populations and

provides information on the disposition. Overall, the majority of patients who discontinued did so due to disease progression.

Table 6: Patient Disposition[20,21]

	PROFILE1005	PROFILE1001*
Efficacy population	136 (Data cutoff February 1, 2011)	119 (Data cutoff September 15, 2010)
Harms population	136 (Data cutoff February 1, 2011)	119 (Data cutoff February 1, 2011)
Patients treated	136	119
Ongoing, n (%)	93 (68.4)	77 (64.7)
Discontinued, n (%)	43 (31.6)	42 (35.3)
Adverse events	6 (4.4)	3 (2.5)
Progressive disease	26 (19.1)	25 (21.0)
Death	6 (4.4)	8 (6.7)
Global deterioration of health status	2 (1.5)	0
Lost to follow-up/Patient decision	1 (0.7)/2 (1.5)	0/1 (0.8)
Other	0	5 (4.2)†

* Data reported for the ALK-positive advanced NSCLC Phase 2 Recommended Dose Cohort
† Clinical progression in 5 patients

New Data:

The pre-planned data cutoff date for 1007 was March 30, 2012. A total of 85 patients (49%) in the crizotinib group and 28 patients (16%) in the chemotherapy group were on treatment at the time of data cutoff. More patients in the chemotherapy arm discontinued treatment prematurely, primarily due to disease progression (Table 7). One hundred and twelve patients (64.4%) in the chemotherapy arm crossed over to receive crizotinib (either in study 1005 or outside of 1005) upon disease progression. Two of these 112 patients did not start any randomized chemotherapy in 1007. Of the remaining 110 patients, 61 had been randomized to pemetrexed (61.6% of patients treated with pemetrexed) and 49 received docetaxel (68.1% of patients treated with docetaxel).

Table 7: Patient Disposition for PROFILE 1007[24]

	Crizotinib	Chemotherapy
Randomized, n (%)	173	174
Received allocated treatment, n (%)	172	171
Safety population, n (%)	172	171
Still on treatment, n (%)	85 (49.1)	28 (16.1)
Discontinued, n (%)	87 (50.3)	143 (82.2)
Adverse events	13 (7.5)	16 (9.2)
Progressive disease*	21 (12.1)	85 (48. 9)
Death	12 (6.9)	4 (2.3)

Table 7: Patient Disposition for PROFILE 1007[24]		
	Crizotinib	Chemotherapy
Global deterioration of health status	37 (21.4)	23 (13.2)
Lost to follow-up/Patient decision	0 (0)	0 (0)
Other	2 (2.1)	11 (6.3)
Crossover to crizotinib	Not applicable	112 (64.4)

*Objective progression or relapse

e) Limitations/Sources of Bias

- The single-arm, non-randomized design for both 1005 and 1001 makes interpreting the efficacy and safety results difficult. In particular, the lack of a randomized comparison treatment group limits the robustness of the preliminary overall survival and progression-free survival results. The overall survival data should likely be considered exploratory given the small sample sizes (no power calculation was provided), and the retrospective, non-randomized design of the survival analysis conducted by Shaw et al.[3]
- Shaw et al.[3] used an unmatched historical control group and, thus, the potential for selection bias and unaccounted for confounding factors need to be considered when interpreting the results. Although most of the patient characteristics were well-balanced between ALK-positive/crizotinib-treated patients and their historical controls (thereby reducing potential selection bias effects), the investigators were not able to compare performance status - a well-established prognostic factor in advanced NSCLC - since this was not consistently assessed in control patients at the start of each line of therapy. Patients from study 1001 had good ECOG performance status (primarily ≤1) and may have had better survival probabilities than controls if controls did not have equally good performance status. Also, there was an imbalance in treatment histories in that the ALK-positive/crizotinib patients had a greater range in number of previous therapies than controls (0-7 versus 1-4, respectively), although the median number of previous therapies was two for each group. Subset analysis of patients receiving second- or third-line therapies may have minimized such bias. Finally, Shaw et al. did not have information on post-crizotinib therapies, which is relevant since 25 of the 82 patients (30%) were known to have received additional chemotherapies after relapsing on crizotinib, which could have provided a survival advantage to the ALK-positive/crizotinib-treated group.
- The adequacy of objective response rate as a surrogate trial endpoint for overall survival is unclear. Objective response rate appears to be correlated with median overall survival, but statistical correlation does not necessarily equate to prediction of survival benefit from response rate. (See section 2.1.4 for more information.) However, the magnitude of the objective response rate in both trials was substantial, and evidence suggests that large response differences might be predictive of a survival benefit.[23] For patient populations as small as approximately 100 (evaluable) patients, a larger effect is needed to judge the likelihood of an overall survival benefit.
- Objective response rate (and progression-free survival) requires tumour measurement via CT or MRI scans. Non-blinded assessment may bias

estimates of effect in favour of crizotinib. In both 1005 and 1001 objective response rate was assessed by both the unblinded investigator (primary outcome) and an independent review panel (retrospectively). There were considerable differences between the response rates as assessed by the investigators versus the independent reviewers (the investigator and independent reviewer agreement rates were 73.5% and 81.9% for studies 1005 and 1001, respectively),[22] suggesting the unblinded assessment by the investigators may have overestimated the response rate and that the more robust estimate of response was by the independent reviewer.

- The single-arm, non-randomized design for both 1005 and 1001 also makes it difficult to assess adverse events attributable to crizotinib since all patients received the same treatment in both studies.
- There is limited data on the efficacy and safety among patients who had not previously received systemic treatment for NSCLC: < 13% of patients in study 1001 had not received systemic therapy and all patients in 1005 had prior treatment. Thus, the data for the use of crizotinib as first-line systemic treatment for advanced NSCLC is not robust.
- ECOG performance status in both studies was predominantly ≤1. Performance status is a well-established prognostic factor in advanced NSCLC. Consequently, the beneficial effects of crizotinib may have been overestimated among a study population with better survival probabilities than typically seen in practice.

New Data:

- The large percentage of patients who crossed over from chemotherapy to crizotinib makes the overall survival findings in 1007 difficult to interpret. There were differential crossover patterns between the two treatment groups, where most 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 chemotherapy making the findings difficult to interpret.
- In addition, the overall survival analyses are immature with only approximately 40% of the total number of deaths required for the final overall survival analysis.
- It is unclear whether the observed statistically significant improvement in progression-free survival and objective response rate with crizotinib versus chemotherapy in 1007 correlates with an overall survival benefit.
- No blinding of investigators or patients in 1007; however, response rates were assessed by Independent Radiology Review which might mitigate potential bias from the lack of investigator blinding
- New and updated efficacy and safety data for crizotinib come from non-peer reviewed sources, except for the published article with updated 1001 data.[1] Largely, the data come from conference abstracts or presentations and clinical summaries provided by the manufacturer in the pCODR resubmission.[24] Consequently, limitations associated with these sources of data prevent a full assessment of the quality of this evidence and caution

should be exercised when drawing conclusions as to the clinical effects of crizotinib

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 22.3 (range: 0.9 to 53.1) weeks and 31.8 (range: 0.9 to 101.7) weeks in 1005 and 1001 for all treated patients, respectively.

Table 8: Summary of Key Outcomes[1,3,20,21,24]

	PROFILE1005 N = 136	PROFILE1001* N = 119
Efficacy		
Overall survival†, median [95% CI] months	Not reported	Not reached
Progression-free survival†, median [95% CI] months	Not reported	10.0 [8.2 to 14.7]
Overall response rate‡, n (%) [95% CI] Complete response Partial response	67 (49.6) [42 to 59] 1 67	71 (61.2) [52 to 70] 2 69
Pooled Harms, n (%)	N = 255	
Deaths	45 (17.6)	
Nonfatal SAEs	62 (24.3)	
AEs	253 (99.2)	
WDAEs	10 (3.9)	

Summary of New Clinical Data				
	PROFILE1007		PROFILE1005 N=261	PROFILE1001* N=149
	Crizotinib (n=173)	Chemo (n=174)		
Efficacy				
Overall survival†, median [95% CI] months HR [95% CI] 1-sided p-value (stratified log rank)	20.3 [18.1 to Not reached] 1.02 [0.68 to 1.54] 0.5394	22.8 [18.6 to Not reached]	Not reported	29.6 [23.1 to Not reached] Not reported
Progression-free survival†, median [95% CI] months HR [95% CI] 1-sided p-value (stratified log rank)	7.7 [6.0 to 8.8] 0.49 [0.37 to 0.64] <0.0001	3.0 [2.6 to 4.3]	8.1 [6.8 to 9.7] Not reported	9.7 [7.7 to 12.8] Not reported
Overall response rate‡, n (%) [95% CI] Complete response Partial response	113 (65.3) [57.7 to 72.4] 1 (<1.0) 112 (64.7)	34 (19.5) [13.9 to 26.2] 0 34 (19.5)	155 (59.8) [53.6 to 65.9] 4 (1.5) 151 (58.3)	87 (60.8) [52.3 to 68.9] 3 (1.7) 84 (59.5)
Harms, n (%)				
Deaths	25 (15)	7 (4)	71 (7.9)§	46 (30.9)

Table 8: Summary of Key Outcomes[1,3,20,21,24]				
SAEs	64 (37.2)	40 (23.4)	(~25)	Not reported¶
AEs	172 (100)	168 (98.2)	245 (93.9)	144 (96.6)
WDAEs	11 (6.4)	17 (9.9)	3 (2.0)	45 (5.0)¶

AE= adverse event; **Chemo**=chemotherapy; **CI** = confidence interval; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event

* Data reported for the ALK-positive advanced NSCLC Phase 2 Recommended Dose Cohort
† Kaplan-Meier method
‡ Response rates were calculated based on the number of evaluable patients: 116 and 135 for study 1005 and 1001, respectively; **New Data**: evaluable population, n=259 and n=143 for study 1005 and 1001, respectively
§ Reported for the full 1005 population only, n=901
¶ Only AEs of grade 3 or 4 reported (n=36, 24.2%)

Efficacy Outcomes

Overall survival

Overall survival was a secondary outcome in both 1005 and 1001, but median overall survival has not been reached. The manufacturer submitted an updated overall survival analysis for 136 patients enrolled in the ALK-positive recommended phase 2 dose cohort of study 1001 in the 60-day clinical data update to the U.S. FDA. The updated median follow-up time was 14.8 months (95% CI: 12.7 to 16.4). Forty out of 136 (29.4%) patients had died with a 12-month survival probability of 75.7% (95% CI: 66.8 to 82.5).[21]

Overall survival of crizotinib-treated, ALK-positive NSCLC patients (ALK-positive/crizotinib) was also evaluated in a retrospective analysis of the first 82 patients treated in study 1001.[3] Shaw et al. conducted several survival comparisons in addition to the overall (non-comparative) survival analysis for the ALK-positive/crizotinib-treated cohort:

1. ALK-positive/crizotinib (non-Korean cohort; n = 56) versus historical case-matched, crizotinib-naïve, ALK-positive NSCLC patients (ALK-positive/control; n = 36). Controls were retrospectively and prospectively identified by investigators at four out of seven study 1001 sites. Because no ALK-positive controls were identified at the Korean study site by the cutoff date of February 10, 2010, controls were compared with the non-Korean ALK-positive/crizotinib cohort.
2. Comparison 1, restricted to patients who received crizotinib in the second- or third-line (n = 30) versus the ALK-positive/control group with any second-line therapy (n = 23). This survival comparison is likely the more appropriate one because the ALK-positive/crizotinib patients had a greater range in number of previous therapies than controls (0-7 versus 1-4, respectively), which could impact survival estimates.
3. The ALK-positive/crizotinib group from comparison 2 (n = 30) versus ALK-negative/EGFR wild-type controls (n = 125) who received second-line therapy.

The results from this retrospective study are presented in Table 9.

Table 9: Summary of Overall Survival, Retrospective Cohort Analysis of PROFILE1001[3]			
	Overall survival*, median [95% CI] months	One-year Survival, % [95% CI]	Two-year Survival, % [95% CI]
ALK-positive / crizotinib-treated n = 82	Not reached [17 to not reached]	74 [63 to 82]	54 [40 to 66]
Non-Korean cohorts			
ALK-positive / crizotinib-treated† n = 56	Not reached [17 to not reached]	71 [58 to 81]	57 [40 to 70]
ALK-positive / crizotinib-naïve n = 36	20 [13 to 26]	72 [54 to 84]	36 [19 to 54]
Second- and/or third-line therapy (non-Korean) cohorts			
ALK-positive / crizotinib-treated‡§ n = 30	Not reached [14 to not reached]	70 [50 to 83]	55 [33 to 72]
ALK-positive / crizotinib-naïve n = 23	6 [4 to 17]	44 [23 to 64]	12 [2 to 30]
ALK-negative / EGFR wild-type n = 125	11 [8 to 15]	NR	NR

ALK = anaplastic lymphoma kinase; **CI** = confidence interval; **EGFR** = epidermal growth factor receptor; **NR** = not reported

* Kaplan-Meier method
† No ALK-positive controls were identified at the Korean study site; hence, the ALK-positive, crizotinib-treated population was limited to non-Koreans
‡ Cohorts restricted to ALK-positive/crizotinib non-Korean patients receiving crizotinib as second- or third-line therapy versus ALK-positive/controls receiving therapy in second-line
§ Cohorts restricted to ALK-positive/crizotinib non-Korean patients receiving crizotinib as second- or third-line therapy versus ALK-negative/EGFR wild-type controls receiving therapy in second-line

Among the 82 ALK-positive/crizotinib patients, median overall survival has not been reached (95% CI: 17 months to not reached). One-year overall survival was 74% (95% CI: 63 to 82), and two-year overall survival was 54% (95% CI: 40 to 66). Survival among 30 ALK-positive/crizotinib patients who were given crizotinib in the second-line or third-line setting was significantly longer than in 23 ALK-positive/controls given any second-line therapy other than crizotinib (hazard ratio 0.36 [95% CI: 0.17 to 0.75]; P = 0.004). ALK-positive/crizotinib patients given second-or third-line crizotinib had significantly better survival compared with 125 ALK-negative/EGFR wild-type controls (hazard ratio 0.49 [95% CI: 0.27 to 0.91]; P = 0.020).[3]

The numbers of patients in these subset analyses were small; hence, caution should be used when making inferences. Nevertheless, there was a significant survival difference favouring the crizotinib group. Restricting the cohorts to comparisons between second- and third-line treatments may help to minimize the selection bias associated with this type of retrospective, non-randomized design. It may also help minimize bias in the survival assessments by control patients who experienced rapidly progressive disease and never received second-line therapy, and by crizotinib-treated patients with more indolent disease who were able to have several lines of therapy before enrolling on a trial.

These findings are suggestive of a strong survival benefit favouring crizotinib, but should be considered exploratory given the limited robustness of the analysis.

Subgroup analyses for overall survival

Subgroup analyses were conducted for the overall survival analysis for the ALK-positive/crizotinib cohort (n = 82). Shaw et al. reported overall survival did not differ across groups (age, sex, smoking history, or ethnic origin); however, given the lack of robustness of these data, conclusions drawn from these analyses should be done with caution.[3]

New Data

As of the data cutoff date for 1007, patients treated with crizotinib had median study treatment duration of 33 weeks (range 3–111) versus 12 weeks (range 3–90) for those in the chemotherapy arm.

A total of 49 (28%) and 47 (27%) deaths, respectively, had been reported in the crizotinib and chemotherapy groups as of the data cutoff date in 1007. The number of deaths at the time of the interim analysis corresponds to approximately 40% of the total number of deaths required for the final overall survival analysis.

As shown in Table 8, crizotinib treatment was not associated with longer survival compared with chemotherapy (median overall survival 20.3 months versus 22.8 months, hazard ratio 1.02 [95% CI: 0.68 to 1.54]). As mentioned previously, this analysis is confounded by crossover from the chemotherapy to crizotinib. The 6-month and 1-year overall survival probabilities were 87% (95% CI: 80.4 to 91.2) and 70% (60.6 to 76.8) for patients randomized to crizotinib and 84% (95% CI: 77.0 to 88.7) and 72% (95% CI: 63.3 to 78.7) for patients randomized to chemotherapy.

The overall survival analysis was adjusted (post hoc) using the Rank Preserving Structural Failure Time (RPSFT) adjustment technique. The resulting crossover adjusted hazard ratio for overall survival of crizotinib versus chemotherapy was 0.83 (95% CI: 0.36, 1.35) as demonstrated in Figure 1.

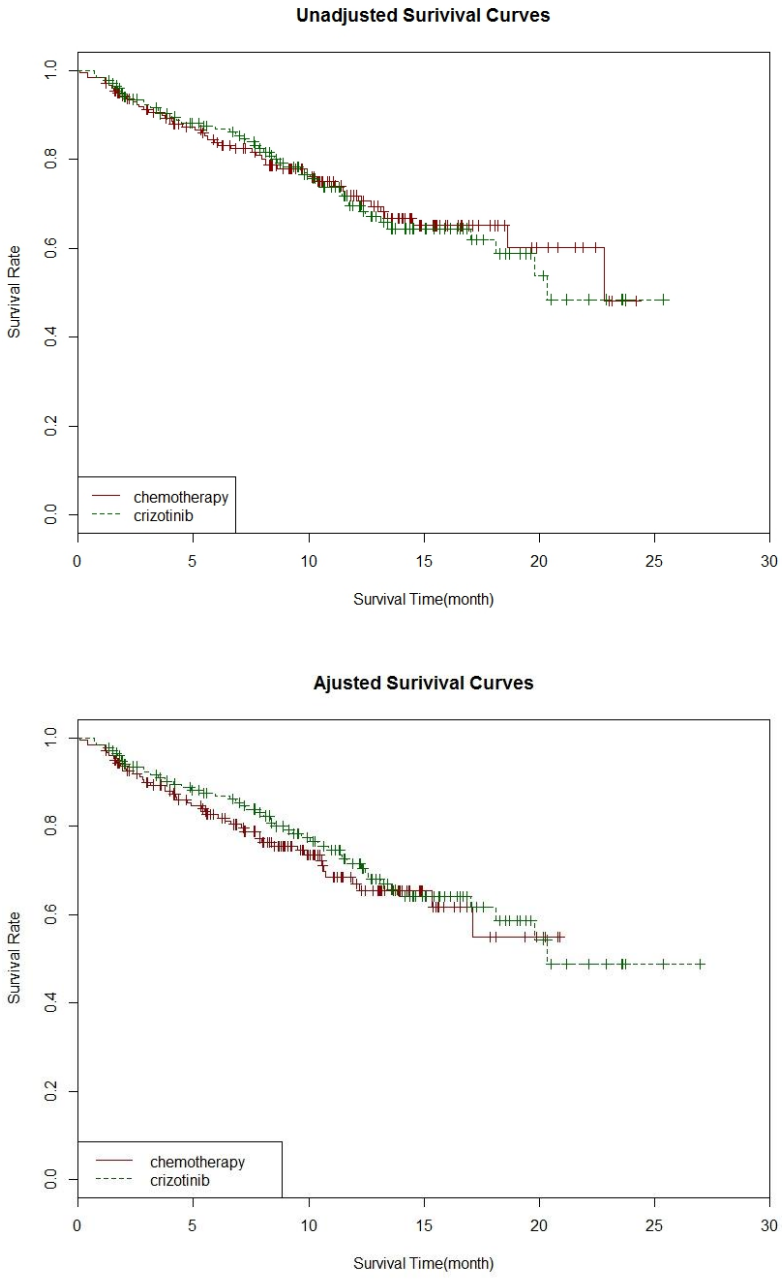


Figure 1: Kaplan-Meier curves for overall survival in PROFILE 1007: crossover adjusted versus unadjusted (RPSFT technique)[24]

Camidge et al.,[1] at the time of publication, reported median overall survival had not been reached after 16.6 months of follow-up in 1001. At the time of data cutoff (June 1, 2011) 46 (30.9%) patients had died; the estimated overall survival at 6 and 12 months was 87.9% (95% CI: 81.3, 92.3) and 74.8% (95% CI: 66.4, 81.5), respectively (Table 8). At a later data cut point (January 2, 2012), overall survival was reached with median of 29.6 months (95% CI: 23.1, upper bound not reached).

No overall survival results were reported for study 1005.

Progression-free survival

Progression-free survival has been estimated as a secondary endpoint from the recommended phase 2 dose ALK-positive cohort of study 1001, and presented in the FDA statistical review. The median progression-free survival was 10 months (95% CI: 8.2 to 14.7; number of events = 50/119, 42%; Table 8).[21]

As with overall survival, the lack of a randomized controlled trial makes it difficult to interpret this outcome.

Subgroup analyses for progression-free survival

No subgroup analyses were reported.

New Data

As shown in Table 8, crizotinib significantly prolonged progression-free survival (primary outcome) compared with chemotherapy, as determined by independent radiology review in study 1007. The median progression-free survival was 7.7 months (100 events [58%]) for patients randomized to crizotinib and 3.0 months (127 events [73%]) for patients randomized to chemotherapy. The hazard ratio comparing crizotinib with chemotherapy was 0.49 (95% CI: 0.37 to 0.64).

Crizotinib significantly prolonged progression-free survival compared with pemetrexed, where the median progression-free survival was 4.2 months (72/99 events [73%]), hazard ratio 0.59 (95% CI: 0.43 to 0.80). Crizotinib also significantly prolonged progression-free survival compared with docetaxel, where the median progression-free survival was 2.6 months (54/72 events [75%]), hazard ratio 0.30 (95% CI: 0.21 to 0.43).

In 1001 (Table 8) at the time of data cutoff, there had been 85 progression-free events (57%; 69 disease progressions and 16 deaths without documented disease progression).[1] The median progression-free survival was 9.7 months (95% CI: 7.7 to 12.8) with a median follow-up for progression-free survival of 16.3 months (95% CI: 13.8 to 18.4). The median progression-free survivals in patients receiving crizotinib first-line (n=24) or second-line of later (n=125) were 18.3 months (95% CI: 8.3, upper bound not reached) and 9.2 months (95% CI: 7.3 to 12.7), respectively.

At the time of analysis of 1005, there had been 167 progression-free events (64%; 140 disease progressions and 27 deaths without documented disease progression). The median progression-free survival was 8.1 months (95% CI: 6.8 to 9.7) with a median duration of follow-up of 48 weeks.

New Data: Subgroup analyses for progression-free survival

The treatment effect of crizotinib across pre-specified subgroups in 1007 was estimated using Cox proportional hazards models and these effects were consistent with the primary analysis for progression-free survival (Table 10). However, despite a trend in favour of crizotinib, the 95% confidence intervals for hazard ratio estimates were overlapping for patients with ECOG performance status of 2 and those with non-adenocarcinoma histology. This may, at least in part, reflect the relatively small number of patients in these subgroups. A subgroup analysis on EGFR mutation 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 10: Progression-free Survival by Subgroup (Pre-specified According to the Systematic Review Protocol)[24]

Subgroup	Progression-free Survival* Hazard Ratios (95% CI)	
	Crizotinib (n=173)	Chemotherapy (n=174)
Sex		
Male	5.5 (4.1 to 9.7)	2.8 (2.1 to 4.3)
Female	8.4 (6.9 to 10.9)	4.0 (2.6 to 5.5)
ECOG performance status		
0/1	8.2 (6.7 to 10.3)	3.8 (2.8 to 4.4)
2	3.2 (1.7 to 8.1)	1.3 (0.9 to 2.1)
Smoking status		
Never smoker	6.7 (5.6 to 8.3)	4.0 (2.1 to 5.5)
Current smoker/Ex-smoker	8.8 (5.6 to 11.2)	2.8 (2.6 to 4.2)
Histologic subtype		
Adenocarcinoma	7.1 (5.6 to 8.8)	3.2 (2.8 to 4.3)
Non-adenocarcinoma	13.9 (4.0 to 16.9)	1.4 (0.5 to 4.4)
EGFR mutation†	Not applicable	Not applicable
Positive		
Negative		

CI = confidence interval; **ECOG** = Eastern Cooperative Oncology Group; **EGFR** = epidermal growth factor receptor

* Based on independent radiology review (IRR) assessment.

† A subgroup analysis on EGFR mutation is not available as this information was not collected.

Quality of life (Patient relevant outcome)

No published data were identified describing quality of life outcomes associated with crizotinib for advanced ALK-positive NSCLC. The FDA review of crizotinib also did not describe the impact of crizotinib on quality of life in this population.

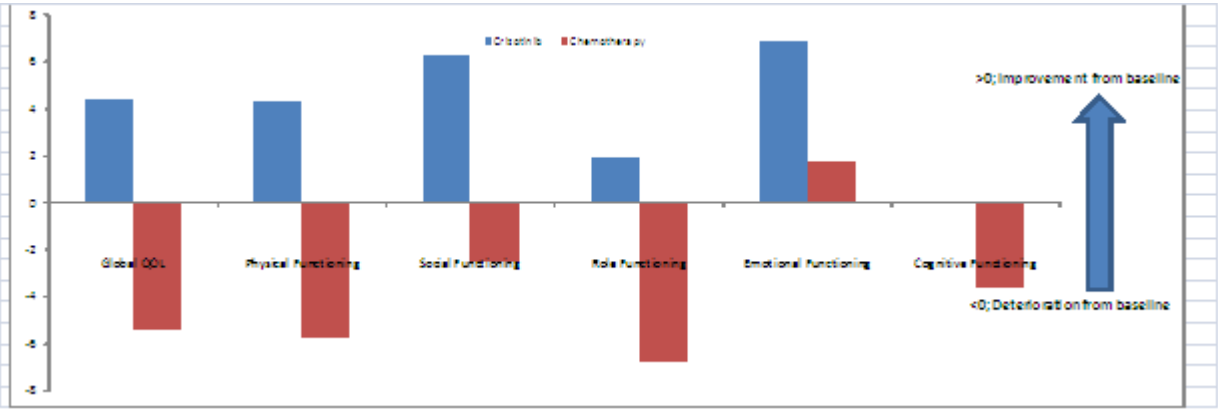
Data on patient-reported outcomes - using the European Organization for the research and Treatment of Cancer Quality of Life Questionnaire, the lung version, from study 1005 were presented at the American Society of Clinical Oncology conference in 2011.[8] According to the abstract presented by Crinò et al., 109 out of 136 patients (80.1%) were evaluated for patient reported outcomes and global quality of life every three weeks using the EORTC QLQ-C30/QLQ-LC13 v.3. A total of four assessments were made over the median nine weeks of treatment, indicating a clinically significant improvement (based on a ≥10 point improvement) in pain, cough, dyspnea, and fatigue. These improvements were reported as identifiable by cycle 2 of crizotinib treatment. A clinically significant increase in constipation was reported by patients. Crinò et al. also reported overall quality of life was "maintained" during the treatment period.[8]

However, the limited details provided in the abstract prevent a full description and critical assessment of this data. In particular, there was no information as to the demographic or clinical characteristics of the subset of evaluable patients. The lack of a randomized comparison group makes it difficult to truly assess the benefits of crizotinib on patient reported outcomes and quality of life.

As the systematic review was nearing completion, the manufacturer provided updated data (data cutoff date of January 2, 2012; n = 901 patients treated) on patient-reported outcomes and global quality of life from the 2012 ASCO Annual Meeting.[53,54] The same pattern of results as described above for patient symptoms and global quality of life was reported. In addition, global quality of life appeared to worsen from treatment cycle 16 to 20. However, the aforementioned limitations of these abstract data prevent a full assessment of the quality of this evidence and caution should be exercised when drawing conclusions as to the impact of crizotinib on quality of life in advanced NSCLC.

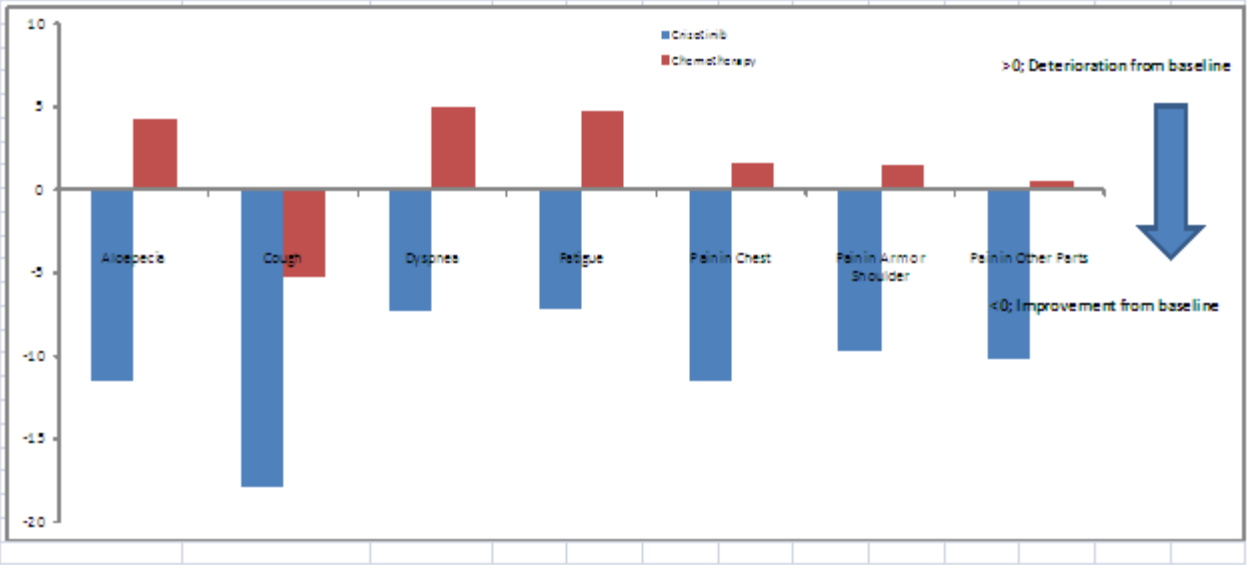
New Data

During the review, pCODR requested in-depth data on patient-reported outcomes from the manufacturer for 1007. However, the data as requested were not available; instead the following figures and high-level results were provided. A significantly greater improvement from baseline in global quality of life was observed in patients treated with crizotinib compared with chemotherapy (estimated difference 9.84, 95% CI: 5.39–14.28; Figure 2). A significantly greater improvement from baseline was also observed in the crizotinib arm compared with chemotherapy in physical functioning (difference 10.11, 95% CI: 6.12–14.10), social functioning (difference 8.76, 95% CI: 3.40–14.12), and role functioning (difference 8.75, 95% CI: 3.57–13.92), and emotional functioning (difference 5.06, 95% CI: 1.06–9.06). Crizotinib was also associated with a significantly greater improvement from baseline in symptoms compared with chemotherapy: cough ($p<0.0001$), dyspnea ($p<0.0001$), fatigue ($p<0.0001$), alopecia ($p<0.0001$), insomnia ($p<0.0001$), and pain ($p<0.0001$); estimated differences between the treatment arms were not reported.



Note: A positive change from baseline is an improvement and a negative change from baseline is deterioration. Change scores calculated based on general linear mixed models

Figure 2: Overall Change from Baseline in Global Quality of Life and Functioning by Treatment in 1007 (EORTC QLQ-C30 and QLQ-LC13)[24]



Note: A negative change from baseline is an improvement and a positive change from baseline is deterioration. Change scores calculated based on general linear mixed models

Figure 3: Overall Change from Baseline in Symptom Scores by treatment arm (EORTC QLQ-C30 and QLQ-LC13)[24]

Updated patient-reported outcome data for 1005 from manufacturer submitted conference posters – from the 2012 ASCO Annual Meeting[53,54] from the original pCODR submission, and two from the 2012 ESMO Annual Meeting poster presenting the same data from the resubmission[24] – were summarized in the original pCODR systematic review (see above).

Overall response rate

The primary endpoint for both study 1005 and 1001 was objective response rate as assessed by the investigators. The response-evaluable population had received crizotinib, as well as a baseline scan and a follow up scan > 6 weeks after starting crizotinib. The number of patients available for independent review was smaller than the number of patients undergoing investigator review (Table 11).

Table 11: Objective Response Rates[20]				
	PROFILE1005†		PROFILE1001†	
	Investigators N = 135	Independent N = 105	Investigators N = 116	Independent N = 105
Objective response rate, n (%) [95% CI]	67 (49.6) [42 to 59]	44 (41.9) [32 to 52]	71 (61.2) [52 to 70]	55 (52.4) [42 to 62]
Complete	1	1	2	0
Partial	67	43	69	55
Duration of response, median weeks [range]*	41.9 [6.1 to 42.1]	33.1 [18.7 to NR]	48.1 [4.1 to 76.6]	58.1 [36.3 to NR]

NR = not reported

* Kaplan-Meier method with censored values

† 136 and 119 patients were enrolled in 1005 and the ALK-positive recommended phase 2 dose cohort of 1001, respectively. N represents the number of evaluable patients and the denominator for calculating the response rate

According to the FDA medical review,[20] 135 patients with ALK-positive advanced NSCLC from study 1005 were evaluable at the time of data cutoff. Based on the investigator assessments, there were one complete and 67 partial responses for an objective response rate of 49.6% (95% CI: 42% to 59%). The objective response by independent review was 41.9% (95% CI: 32% to 52%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

One hundred and sixteen patients with ALK-positive advanced NSCLC were evaluable on study 1001 at the time of data cutoff. Based on the investigator assessments, there were 2 complete and 69 partial responses for an objective response rate of 61.2% (95% CI: 52% to 70%).[20] The objective response rate by independent review was 52.4% (95% CI: 42% to 62%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Subgroup analyses for overall response rate

The protocol for this review identified several pre-specified subgroups of clinical interest: baseline treatment status for advanced/metastatic NSCLC; histologic type; ECOG performance status; sex; smoking status; and EGFR mutation status. On subgroup analysis, there was no clear difference in objective response rate, as presented in the FDA review (Table 12).[20]

Table 12: Objective Response Rate by Subgroup (Pre-specified According to the Systematic Review Protocol)[20,21]		
Subgroup	PROFILE1005 Objective Response Rate % (n) [95% CI] N = 135*	PROFILE1001 Objective Response Rate % (n) [95% CI] N = 116*
Sex		
Male	42.2 (27/64) [29.9 to 55.2]	61.0 (36/59) [47.4 to 73.5]

Table 12: Objective Response Rate by Subgroup (Pre-specified According to the Systematic Review Protocol)[20,21]		
Subgroup	**PROFILE1005 Objective Response Rate % (n) [95% CI] N = 135***	**PROFILE1001 Objective Response Rate % (n) [95% CI] N = 116***
Female	56.3 (40/71) [44.1 to 68.1]	61.4 (35/57) [47.6 to 74.0]
ECOG performance status		
0	54.1 (20/37) [36.9 to 70.5]	53.8 (21/39) [37.2 to 69.9]
1	52.1 (38/73) [40.0 to 63.9]	62.9 (39/62) [49.7 to 74.8]
2	36.0 (9/25) [18.0 to 57.5]	78.6 (11/14) [49.2 to 95.3]
3	NA	0 (0/1)
Smoking status		
Never smoker	51.7 (47/91) [40.9 to 62.3]	63.1 (53/84) [51.9 to 73.4]
Ever or Current smoker	45.5 (20/44) [30.4 to 61.2]	56.3 (18/33) [37.7 to 73.6]
Histologic subtype	NR	NR
Adenocarcinoma		
Squamous cell carcinoma		
Adenosquamous carcinoma		
NSCLC NOS		
Number of prior chemotherapy regimens for advanced/metastatic disease		
0	NA	85.7 (12/14) [57.2 to 98.2]
1	46.2 (6/13) [19.2 to 74.9]	54.6 (18/33) [36.4 to 71.9]
2	62.2 (23/37) [44.8 to 77.5]	60.0 (12/20) [36.1 to 80.9]
3	43.2 (16/37) [27.1 to 60.5]	76.5 (13/17) [51.1 to 93.2]
≥4	45.8 (23/48) [31.4 to 60.8]	50.0 (16/32) [31.9 to 68.1]
EGFR mutation	NR	NR
Positive		
Negative		

CI = confidence interval; **ECOG** = Eastern Cooperative Oncology Group; **EGFR** = epidermal growth factor receptor; **NA** = not applicable; **NSCLC** = non-small cell lung cancer; **NR** = not reported

* 136 and 119 patients were enrolled in 1005 and the ALK-positive recommended phase 2 dose cohort of 1001, respectively. N represents the number of evaluable patients and the denominator for calculating the response rate

The objective response rates ranged from 36% to 62% in Study 1005 and 50% to 86% in Study 1001. In Study 1005, females had higher objective response rates than males (56% versus 42%). However, this difference was not observed in Study 1001. Patients with ECOG performance status of 2 had a much lower response rate than those with a performance status ≤1 in study 1005. The reverse was observed for study 1001, where patients with a performance status of 2 had a better tumor response versus those with lower performance status. Given the small sample sizes across subgroups, however, caution should be used when drawing conclusions as to the significance of these results.

New Data:

The objective response rates reported in the updated data for 1001 (60.8%) and 1005 (59.8%) were similar across studies and consistent with those reported in the original pCODR systematic review (Table 8). In 1007, the objective response rate for patients randomized to crizotinib in 1007 was 65.3% (95% CI: 58 to 72) and for patients randomized to chemotherapy was 19.5% (95% CI: 14 to 26); an absolute difference of almost 46% (objective response rate ratio of 3.4 [95% CI: 2.5 to 4.7] in

favour of crizotinib). The respective objective response rates for pemetrexed and docetaxel were 29.3% (95% CI: 21 to 39) and 6.9% (95% CI: 2 to 16).

New Data: Subgroup analyses for overall response rate

The objective response rates with crizotinib across pre-specified subgroups in 1001 were consistent with the primary analysis for objective response rates. No subgroup data on objective response rates were reported for 1005 or 1007.

Harms Outcomes

Data regarding adverse events were sparsely reported in the literature for studies 1005 and 1001. Consequently, data for this section of the systematic review were extracted primarily from the FDA medical review of crizotinib.[20] The FDA medical review pooled data from both studies for deaths and nonfatal serious adverse events (SAEs), but study-level data were presented for other adverse events (AEs).

Serious adverse events (Patient relevant outcome)

According to the FDA medical review,[20] 45 deaths occurred among patients receiving crizotinib for ALK-positive NSCLC in studies 1005 and 1001 combined. Among the 45 patients, 32 deaths were due to disease progression and 13 were due to an AE. Adverse events that occurred within 28 days of crizotinib administration and that were associated with death were largely respiratory-related and included: pneumonia (n = 2); septic shock/disseminated intravascular coagulation (n = 2); and one case each of pneumonitis, acute respiratory distress syndrome, hypoxia, empyema, pulmonary hemorrhage, and death NOS. However, given the single-arm study design in advanced NSCLC, it is unclear whether these respiratory events were related to crizotinib or to the underlying disease.

Nonfatal SAEs occurred in 24.3% of patients receiving crizotinib in studies 1005 and 1001 combined. Grade 3 to 4 AEs occurred in 40.8% of the 255 patients in both studies. Events that occurred in greater than five percent of patients included elevated liver transaminases (AST/ALT), dyspnea, pneumonia, and neutropenia, according to the FDA medical review.[20]

Crizotinib may cause QT prolongation. According to the FDA assessment, approximately 1% of patients from studies 1005 and 1001 developed a QTcF > 500 ms and 3% of patients had an increase in QTcF > 60 ms.[20]

New Data

In 1007 safety population, 25 deaths occurred among patients receiving crizotinib compared with seven deaths among patients receiving chemotherapy (Table 13). Among the 25 deaths in the crizotinib arm, 13 were due to disease progression with an additional two cases having evidence of death due to disease progression (NSCLC, respiratory failure). Three deaths were considered crizotinib-related (arrhythmia, interstitial lung disease, and pneumonitis) with an additional two deaths (death, sudden death) considered as potentially treatment-related. One death was considered chemotherapy-related.

Table 13: Serious Adverse Events by Treatment Arm in PROFILE 1007, Safety Population[24]		
SAEs, n (%)	Crizotinib (n=172)	Chemotherapy (n=171)
Total deaths	**25 (15)**	**7 (4)**
Total SAEs	**64 (37.2)**	**40 (23.4)**
Disease progression	13 (7.6)	3 (1.8)
Pneumonia	7 (4.1)	3 (1.8)
Pulmonary Embolism*	6 (3.5)	3 (1.8)
Interstitial Lung Disease*	5 (2.9)	0 (0.0)
Dyspnea*	4 (2.3)	2 (1.2)
Neutropenia*	3 (1.7)	14 (8.2)
Elevated Transaminases*	2 (1.2)	0 (0.0)
Neuropathy*	2 (1.2)	0 (0.0)
Anemia*	1 (0.6)	3 (1.8)
Cough	1 (0.6)	0 (0.0)
Hepatotoxicity*	1 (0.6)	0 (0.0)
Thrombocytopenia*	0 (0.0)	1 (0.6)

* Denotes pre-specified clustered terms

Overall, SAEs occurred in 37.2% of patients receiving crizotinib compared with 23.4% of patients receiving chemotherapy. SAEs occurring in at least 5% of patients in the crizotinib versus chemotherapy arm included disease progression (7.6% versus 1.8%) and neutropenia (1.7% versus 8.2%).

Adverse events (Patient relevant outcome)

Adverse events (AEs) of any grade occurring in ≥25% of patients were extracted from the FDA medical review and are summarized in Table 14.[20] Adverse events were collected in 1005 using Common Terminology Criteria (CTC) for adverse events version 4 and in 1001 using CTC version 3. Despite this, the prevalence of various AEs was similar in the two studies.

Table 14: Most Common (Incidence ≥25%) Adverse Events (AEs) with Crizotinib[20]		
AEs, n (%)	PROFILE1005 N = 136	PROFILE1001 N = 119
Total AEs	**136 (100)**	**117 (98.3)**
Nausea	86 (63.2)	59 (49.6)
Visual disorder*	83 (61.0)	76 (63.9)
Vomiting	68 (50.0)	48 (40.3)
Diarrhea	67 (49.3)	57 (47.9)
Edema/Peripheral edema	54 (39.7)	43 (36.1)
Constipation	53 (39.0)	45 (37.8)
Fatigue	50 (36.8)	30 (25.2)
Decreased appetite	42 (30.9)	29 (24.4)
Cough/Productive cough	38 (27.9)	16 (13.4)
Dyspnea/Exertional dyspnea	35 (25.7)	22 (18.5)
Dizziness†	26 (19.1)	35 (29.4)
Esophageal disorder‡	21 (15.4)	30 (25.2)

* Includes diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, and visual brightness
† Includes balance disorder, dizziness postural, and presyncope
‡ Includes dyspepsia, dysphagia, epigastric discomfort/burning, esophagitis, esophageal obstruction, pain, spasm, and ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis

A substantial number of patients from both studies required dose modification, with 36.0% and 45.4% of patients from 1005 and 1001, respectively, having treatment interrupted. Additionally, 44.1% and 29.4% of patients from 1005 and 1001 required dose reductions during treatment.[20]

Collectively, the organ class group gastrointestinal disorders — primarily nausea, vomiting, diarrhea, and constipation — were the most commonly reported AEs in both studies.[20] Visual disorders were reported in the majority of patients (163 out of 255; 63.9%), mostly of grade 1 severity with no need for dose discontinuation or reduction.

New Data

Overall AEs reported in 1007 and the updated 1001 and 1005 data were consistent with those reported in the original pCODR systematic review.

The total AEs (all grades) observed in the crizotinib and chemotherapy arms were 100% and 98.2%, respectively, in study 1007 (Table 15). Some notable differences in reported AE percentages occurred in study 1007 when comparing crizotinib versus chemotherapy treatment, namely diarrhea (59.9% versus 19.3%), vision disorder (59.9% versus 9.4%), nausea (54.7% versus 37.4%), vomiting (46.5% versus 17.5%), constipation (42.4$ versus 22.8%), elevated transaminases (38.4% versus 14.6%), edema (31.4% versus 15.8%), dizziness (16.3% versus 7.0%), rash (8.7% versus 17.0%), and alopecia (8.1% versus 20.5%). Although hepatotoxicity occurred overall infrequently, relatively more instances were reported in the crizotinib arm (n=5, 2.9%) than for chemotherapy (n=1, 0.6%). Grade 3 to 4 AEs were similar between the crizotinib and chemotherapy arms, except for elevated transaminases occurring in 15.7% of patients receiving crizotinib compared with 2.3% receiving chemotherapy. No cases of grade 3 or 4 hepatotoxicity were reported.

Table 15: Adverse Events (Occurring in ≥5% of Patients in Either treatment Group) by Treatment Group in PROFILE 1007, Safety Population[24]		
AEs, n (%)	Crizotinib (n=172)	Chemotherapy (n=171)
Total AEs	**172 (100)**	**168 (98.2)**
Diarrhea	103 (59.9)	33 (19.3)
Vision Disorder*	103 (59.9)	16 (9.4)
Nausea	94 (54.7)	64 (37.4)
Vomiting	80 (46.5)	30 (17.5)
Constipation	73 (42.4)	39 (22.8)
Elevated Transaminases*	66 (38.4)	25 (14.6)
Edema*	54 (31.4)	27 (15.8)
Decreased appetite	47 (27.3)	45 (26.3)
Neutropenia*	47 (27.3)	39 (22.8)
Headache	32 (18.6)	26 (15.2)
Pyrexia	30 (17.4)	32 (18.7)
Anemia*	29 (16.9)	30 (17.5)
Dizziness	28 (16.3)	12 (7.0)
Asthenia	25 (14.5)	32 (18.7)
Dyspnea*	23 (13.4)	32 (18.7)
Rash	15 (8.7)	29 (17.0)
Alopecia	14 (8.1)	35 (20.5)
Pulmonary Embolism*	10 (5.8)	4 (2.3)

* Denotes pre-specified clustered terms

The overall frequency of AEs in the updated 1005 and 1001 data were 93.9% (245/261) and 97% (144/149), respectively. As observed in 1007 and in the original pCODR submission, the most frequently occurring AEs (≥25% of patients) were vision disorder and gastrointestinal-related (nausea, vomiting, diarrhea, constipation).

Withdrawals due to adverse events

According to the FDA medical review, a total of 5.1% (7/136) and 2.5% (3/119) of patients treated with crizotinib in studies 1005 and 1001, respectively, discontinued treatment due to AEs. The most frequent AEs associated with discontinuation in both studies were elevated transaminases (ALT) and pneumonitis.[20]

New Data

Table 16 summarizes the adverse events leading to withdrawal by treatment group (occurring in >1 patient) in 1007. Interstitial lung disease was the leading adverse event leading to withdrawal among crizotinib-treated patients, whereas febrile neutropenia was most commonly reported in the chemotherapy arm. As reported during the original pCODR review, elevated hepatic transaminases were also reported more frequently for crizotinib patients who discontinued early.

Table 16: Withdrawals due to Adverse Events (Reported in >1 Patient) by Treatment Group in 1007 Safety Population[24]		
	Crizotinib (n=172)	Chemotherapy (n=171)
Total WDAE, n (%)	**11 (6.4)**	**17 (9.9)**
Interstitial lung disease	3 (1.7)	0
Elevated ALT	2 (1.2)	0
Elevated AST	2 (1.2)	0
Febrile neutropenia	0	3 (1.8)
Asthenia	0	2 (1.2)
ALT=alanine aminotransferase; **AST**=aspartate aminotransferase; **WDAE**=withdrawal due to adverse event		

In 1001, no additional patients withdrew due to adverse events versus the original pCODR submission.

Withdrawals due to adverse events were provided for the updated overall population, not the mature population in 1005: 45/901 (5.0%).

6.4 Ongoing Trials

Two key ongoing trials were identified, both of which were mandated by the U.S. FDA to confirm the post-marketed clinical benefits of crizotinib treatment and to fulfill the requirement for the recommended accelerated approval:

Study A8081007 (NCT00932893): Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus standard of care (pemetrexed or docetaxel) in patients with advanced NSCLC harbouring a translocation or inversion event involving the anaplastic lymphoma kinase gene locus

- Eligible patients will have received one prior platinum-based regimen. There is one interim analysis planned at 60% of events (with alpha = 0.0038). At the final analysis (n = 318) it will have 90% power to detect an improvement in the primary endpoint, progression-free survival, from 2.9 to 4.4 months (with alpha = 0.025). The study will have 80% power to detect an improvement in overall survival (a secondary endpoint) from 8 to 11.5 months (with alpha = 0.025);
- PROFILE 1007 has been completed and preliminary information released by the manufacturer suggests crizotinib significantly improved progression-free survival when compared with pemetrexed or docetaxel in previously treated patients with advanced NSCLC.[56] However, actual data have yet to be reported or published.

- Study A8081014 (NCT01154140): Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus cisplatin/pemetrexed or carboplatin/pemetrexed in previously untreated patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the anaplastic lymphoma kinase gene locus
  - The study is expected to enroll at least 334 patients to achieve 85% power to detect an improvement in progression-free survival (the primary endpoint) from 6 to 9 months (with alpha = 0.025).

pCODR requested efficacy and safety data for both study 1007 and study 1014 from the manufacturer during the systematic review, but was informed the data were unavailable at the time of the request.

Following Resubmission to pCODR

Preliminary reports presenting data from Study A8081007 (NCT00932893, or PROFILE1007) were included in the manufacturer's resubmission. Study A8081014 (NCT01154140) remains ongoing.

One additional ongoing key trial was identified examining crizotinib for ALK-positive NSCLC:

- Study A8081029 (NCT01639001): Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus cisplatin/pemetrexed or carboplatin/pemetrexed in previously untreated East Asian patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the anaplastic lymphoma kinase gene locus
    - The study is expected to enroll at least 200 ALK-positive NSCLS East Asian patients. The primary outcome is progression-free survival over a 36-month period
    - The study is currently recruiting participants.

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.[19] Several different molecular methodologies may be used to detect these rearrangements, including fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), chromogenic in situ hybridization (CISH), or reverse transcriptase polymerase chain reaction of cDNA (RT-PCR). Of these, FISH is considered the gold standard assay and a test using this approach has received market authorization in North America.

Description of the Vysis ALK Break Apart FISH Assay

The Vysis ALK Break Apart FISH Probe Kit (here also referred to as 'ALK FISH') is intended to detect rearrangements involving the ALK gene via fluorescence in situ hybridization. The test is performed on formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens using a paraffin pretreatment reagent kit.[57] ALK FISH is the only companion diagnostic test approved by Health Canada.[18] The ALK FISH probe kit is manufactured by Abbott Molecular Inc.[28] and the test was used to diagnose patients with ALK-positive NSCLC in the PROFILE1001 and 1005 clinical trials examining the safety and efficacy of crizotinib for advanced NSCLC.[2,4-9]

The following materials are included in the probe kit provided by the manufacturer:[57,58]

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

ALK FISH is conducted on FFPE lung cancer tissue with either resection or cytology specimens. FFPE is the most common method in processing and storing tumor specimens in pathology laboratories.[28] Therefore, the majority of NSCLC patients should have tumor tissue suitable for the test. One unstained slide cut from the FFPE block is sufficient for ALK FISH testing.[28] A single ALK- FISH kit can analyze up to 10 samples (9 patient samples plus 1 control) per hybridization. It has limited automation and requires manual pipetting and slide preparation; thus, the assay is highly dependent on the qualifications and experience of the technician conducting the assay. ALK FISH requires a fluorescence microscope to detect the fluorescent split signal (which is not routinely used in pathology), and the signals are labile and rapidly fade over time. Furthermore, reading the split signal requires a pathologist. The hybridization takes 48 hours to obtain results.

The most important advantage of ALK FISH is that it is capable of detecting any ALK rearrangements, including potentially rare or uncharacterized ALK rearrangements.[28] As suggested in the literature, however, ALK FISH as a routine screening test in large-scale NSCLC patients has several limitations.[28,31] First, testing and interpretation of results require special technical training or resources, which may not be available in most pathology laboratories. Second, the interpretation of the testing results can be challenging; for example, due to intra-chromosomal deletion and inversion or variability in the precise fusion of ALK with partner proteins. Also, the short duration of the fluorescence signal and the need to use a specialized camera to record the results complicates the assessment. As well, morphology can be difficult to determine using FISH. Third, the cost associated with ALK FISH testing is a consideration and in some jurisdictions, may be considered prohibitive. For example, in one published estimate from the United States, the total cost to identify one ALK-positive patient could add up to $20,000, when the prevalence of ALK rearrangements is assumed to be approximately 5% in all NSCLC patients, and the cost of ALK FISH testing is $1,000 per patient.[28] Anaplastic lymphoma kinase gene rearrangements are uncommon (2%–5%) in NSCLC patients, with approximately 400–500 ALK-positive cases occurring each year in Canada.[17,18] Assuming the same total cost to identify one ALK-positive patient, the costs for identifying all ALK-positive patients in Canada could be up to $8,000,000 to $10,000,000 per year. Additional information provided on ALK FISH testing stated that the commercial price for the Vysis ALK Break Apart FISH Probe Kit is CAN$ 2700 per kit, including sufficient amounts of reagents to process 20 assays.[59] The cost of the test, which includes the total test kit, technical and professional costs per specimen, is estimated to be CAN$ 530, assuming testing is concentrated in high quality, high volume facilities. A full costing estimate, taking into account all costs associated with the test, remains necessary to evaluate the economic impact of the ALK FISH test. However, this is outside the scope of this Supplemental Question.

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

There are currently no clinically validated or regulatory approved alternative methods available to ALK FISH for routine screening and diagnosis of ALK-positive NSCLC. To date, IHC represents the most promising alternative to ALK FISH in terms of reliability and cost. IHC is a routine and affordable technique used in regular pathology laboratories. Unlike FISH, which determines ALK status by detection of gene rearrangement, IHC achieves this by detection of ALK mutation protein overexpression. It has been suggested that IHC be used as the initial screening tool for

patients with ALK-positive NSCLC, with ALK FISH as confirmatory diagnosis for patients identified as ALK-positive based on IHC.[28-31]

In 2012, a French study evaluated the validity of a commercially available IHC test by comparing it with ALK FISH (Vysis ALK Break Apart FISH Probe Kit) in testing for ALK gene rearrangement in lung adenocarcinomas in routine practice.[31] A total of 441 biopsies and surgical specimens were analyzed. IHC testing was conducted using one of three commercially available monoclonal ALK antibody (Clone 5A4, Ab 17127; 1:50 dilution; Abcam, Cambridge, UK) and an amplification system. The study reported the validity results from a selected 100 specimens that had been subjected to both IHC and ALK FISH testing. As shown in Table 11, the sensitivity and specificity of IHC were 90.5% versus 98.3%, respectively. Of note, 19 out of 100 cases had ALK FISH testing results not interpretable due to inappropriate fixation, a decalcification process, or the presence of <20% of malignant cells on the slides.

Table 11: Validity of Immunohistochemistry (IHC) Test Compared with ALK FISH[31]

	FISH Positive (n = 21)	**FISH Negative (n = 60)**	**FISH Not Interpretable (n = 19)**
IHC Positive (n = 27)	19/21 (90.5%)	1/60 (1.7%)	7/19 (36.8%)
IHC Doubtful (n = 2)	2/21 (9.5%)	0	0
IHC Negative (n = 71)	0	59/60 (98.3%)	12/19 (63.2%)

ALK = anaplastic lymphoma kinase; **FISH** = fluorescence in situ hybridization; **IHC** = immunohistochemistry

In 2011, Yi et al. conducted a study in patients with lung adenocarcinomas (n = 101) at the Mayo Clinic in the United States.[30] The study explored an IHC testing score algorithm using a monoclonal antibody (Dako; clone ALK1; 1:100 dilution). The sensitivity and specificity of IHC scoring for detecting ALK rearrangements were 90% and 97.8%, respectively, when compared with ALK FISH. Similarly, Rodig et al. reported a sensitivity and specificity of 80% and 100%, respectively, for the detection of ALK rearrangements when using IHC with tyramide amplification in patients with lung adenocarcinomas (n = 358).[60] Of note, both studies used the most commonly used monoclonal antibody in pathology laboratories.

In general, IHC is a rapid and affordable method preferred by pathologists for routine screening and diagnosis. IHC is a mostly automated assay that can analyze from 30 to 60 samples (depending on the autostainer) and it takes three to five hours to obtain results. Unlike ALK FISH, the stain is permanent and can be stored in the laboratory and examined multiple times. 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).[28] The major disadvantage for IHC is lower sensitivity versus ALK FISH; the often low-level expression of ALK fusion proteins in ALK rearrangements requires a more sensitive assay, such as combining IHC with an amplification process or the IHC score algorithm used by Yi et al.. In addition, IHC is sensitive to tissue fixation, which could lead to false-negative results and decreased sensitivity in detecting ALK arrangements.[28] In addition, there is no consensus as to which of the three commercially available IHC antibodies is the most sensitive and specific in identifying ALK gene rearrangements.

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.[61] 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.[61] 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 (κ = 0.92) and between observers (κ = 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%).[61] 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 (κ = 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.

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.[28]

Implementation of ALK Mutation Tests

Since ALK mutation testing for crizotinib treatment is quite new, there is limited information on its implementation. A decision analytic protocol requested by the medical services advisory committee (MSAC) in Australia regarding the implementation of a molecular diagnostic test for another targeted cancer therapeutic highlighted the following general issues:[62]

- in-house mutation tests should be performed in laboratories accredited for genetic testing in humans. Since laboratories accredited are unlikely located in rural or remote areas, tissue biopsies or specimens would need to be sent to accredited laboratories in metropolitan areas or large regional laboratories;
- the tissue sample for analysis would be selected by an anatomical pathologist and macro-dissected or micro-dissected as required;
- competence to perform the test would need to be monitored through quality assurance programme (QAP) and a pilot QAP would be needed;
- repeat testing or re-biopsying may be required if there is insufficient tumour material to provide a definitive result.

This highlights the multiple factors and challenges to consider, including identifying the clinician who should be responsible for requesting a genetic test, delays in testing and result reporting, as well as the quality of tissue samples, and appropriate storage and transfer of the samples to the laboratories, when adopting molecular diagnostics for targeted therapies into a health system.

The estimated costs associated with different screening tests in a U.S. health care setting and their ability to detect true positive rearrangements are summarized in Table 17.[32] Testing prices were based on laboratory charges including technical and professional fees, while costs for tissue acquisition, storage and shipments were not included. No published estimates in a Canadian health care setting are available.

Table 17: Summary of Costs Associated with FISH, IHC, and RT-PCR for Identifying ALK Gene Rearrangements[32]

Tests	Estimated Unit Price (U.S. Dollars)	Effectiveness Relative to FISH* (%)
FISH	$1400	100
RT-PCR	$875	70
IHC (3+ cutpoint only)†	$600	80
ALK = anaplastic lymphoma kinase; **FISH** = fluorescence in situ hybridization; **IHC** = immunohistochemistry; **RT-PCR** = reverse transcriptase polymerase chain reaction		

* ALK FISH testing is taken as the reference standard for positivity.
† This calculation based on 3+ IHC staining is the level associated with no false-positive results.

The above information is limited chiefly by use of estimated commercial charges for testing derived from a single institution in the U.S., thereby reducing its transferability to the Canadian health care setting. A costing estimate for the Canadian setting, taking into account all additional costs associated with the conduct of these tests, would be necessary to fully understand the economic impacts of each type of test; such an exercise is, however, outside the scope of this Supplemental Question.

As mentioned previously, given the cost and potential barriers to implementing ALK FISH testing, it has been suggested that IHC be used as the initial screening tool for patients with ALK-positive NSCLC, with ALK FISH as confirmatory diagnosis for patients identified as ALK-positive based on IHC.[28-31] Figure 4 presents a proposed system for assessing ALK status using IHC as the initial screening method with reflex ALK FISH testing.

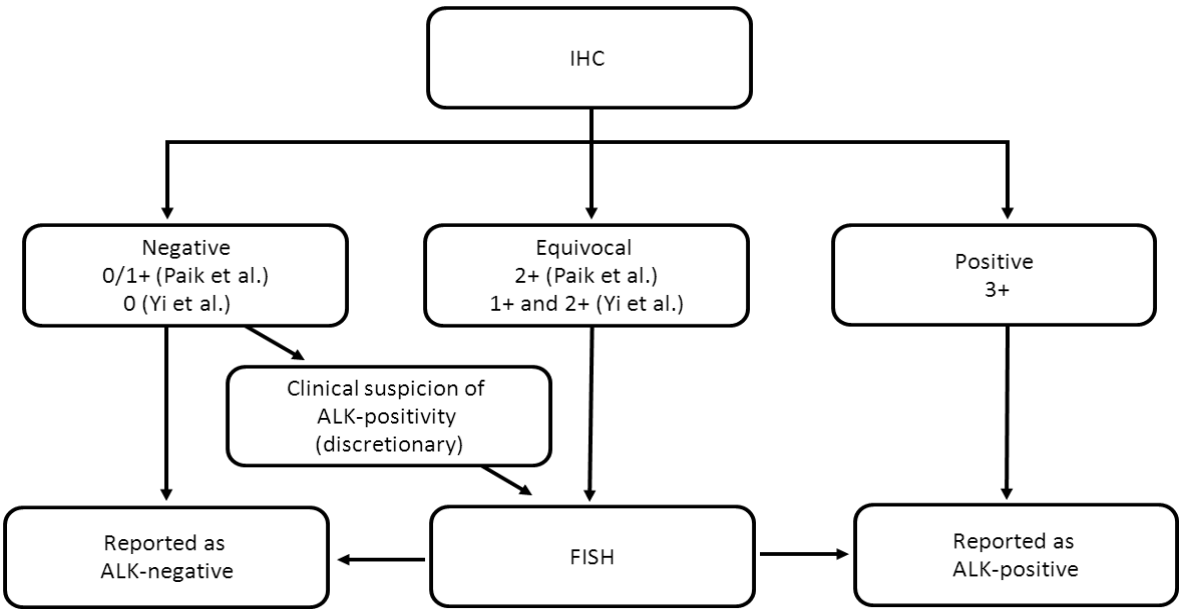


Figure 4: Proposed two-tier system for measuring ALK status in NSCLC. Adapted from Paik et al. and Yi et al.[29,30] Provided by Pfizer[63]

According to Pfizer, a pan-Canadian ALK diagnostic project (CALK) was initiated in 2011 with an overarching objective to validate ALK detection methods with the intention of standardizing ALK assays in Canada and to develop an algorithm for lung cancer biomarker testing. The assays that are being validated are FISH and IHC. A total of 13 centers across Canada, as well as one centre in each of the U.S. and Japan, are participating in the project. The project is now .[63]

7.1.3 Summary

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 for identifying ALK-positive NSCLC patients who should receive targeted systemic therapy with crizotinib.[19] The Vysis assay was used to identify eligible patients for inclusion into the clinical trials for crizotinib in advanced NSCLC, PROFILE1001 and 1005.[2,4-9] 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.[28] However, the conduct of the test and interpretation of the test results require special technical training that is currently not available in routine laboratory practice throughout Canada and cost is a consideration. Hence, although ALK FISH is commercially available, without publicly disclosable information on which laboratories may be prepared to process specimen, it is not possible to confirm if the test is readily accessible to all patients with NSCLC across the jurisdictions. 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 proposed, 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.[29-32] A multicentre pan-Canadian study is ongoing to examine the appropriateness of IHC and FISH as tests to identify ALK gene rearrangements in NSCLC patients and, therefore, potential recipients of crizotinib.

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.pcodr.ca).

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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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.pcodr.ca). 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

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to 2012 December 31, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	*"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 PF2341066 or PF 2341066 or PF02341066 or 877399-52-5).ti,ab.	621
2	1 use oemezd	395
3	(Crizotinib* or Xalkori* or "PF 02341066" or PF2341066 or PF 2341066 or PF02341066 or 877399-52-5).ti,ab,ot,sh,hw,rn,nm.	1129
4	3 use pmez	259
5	2 or 4	654
6	remove duplicates from 5	446

2. Literature search via PubMed

Search	Query	Items found
#3	Search **#3 AND #4**	17
#2	Search **publisher[sb]**	421039
#1	Search **crizotinib [Supplementary Concept] OR Crizotinib[tiab] OR Xalkori[tiab] OR PF 02341066[tiab] OR PF2341066[tiab] OR PF02341066 OR PF 2341066 OR 877399-52-5[rn]**	242

3. Cochrane Library

Cochrane Database of Systematic Reviews: Issue 12 of 12, December 2012

- There are 0 results from 0 records for your search on 'Crizotinib* or Xalkori* or PF 02341066 or PF2341066 or PF02341066 OR PF 2341066 OR 877399-52-5 in title abstract keywords '

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: Xalkori or crizotinib

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: Search terms: Xalkori or crizotinib

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: Xalkori or crizotinib / last 5 years

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