pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

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

May 23, 2019

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1 GUIDANCE IN BRIEF

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 (Xalkori) for ROS1- positive advanced NSCLC. 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding crizotinib (Xalkori) for ROS1- positive advanced NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from registered clinicians; and supplemental issues relevant to the implementation of a reimbursement decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on crizotinib (Xalkori) for ROS1- positive advanced NSCLC a summary of submitted Provincial Advisory Group Input on crizotinib (Xalkori) for ROS1- positive advanced NSCLC, and a summary of submitted registered clinician input on crizotinib (Xalkori) for ROS1- positive advanced NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

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

The Health Canada indication for crizotinib is as monotherapy for use in patients with ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC. The efficacy in patients with ROS1 positive NSCLC was based on objective response rate (ORR) and duration of response (DR) in a single arm study with a limited number of patients (N=53) including 7 patients who were considered treatment naïve.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two clinical trials. The results of the PROFILE 1001 (N = 53) and Ox ONC (N= 127) trials are as follows:

PROFILE 1001[1-3]

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

The primary endpoint of the PROFILE 1001 ROS1 expansion study was objective response rate (ORR), determined according to the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety.

A total of 53 eligible patients with ROS1-positive NSCLC were enrolled. The median age for the ROS1 expansion cohort was 55 years (range 25 to 81). The majority of patients were White (56.6%) or Asian (39.6%), and never smokers (75.5%). All patients presented with measurable disease; 96.2% had adenocarcinoma histology; and 86.8% had received at least one prior line of treatment.

Efficacy

The key efficacy outcomes of the PROFILE 1001 trial (ROS1 Positive expansion cohort)are presented in Table 1.1.

As of 30-November-2014 data cut-off date, after median follow-up of 25.4 months:[2,3]

- ORR was 70% (95% CI 56, 82), including five (9.4%) patients with complete response, 32 (60.4%) patients with a partial response, and 11 (20.8%) patients with stable disease. In the subgroup of seven patients with no prior advanced/metastatic therapies, the ORR was estimated to be 85.7% (95% CI 42.1, 99.6).
- The median TTR was 7.9 weeks (range 4.3 to 32.0); and the estimated median DOR was 17.6 months (range; 2.8 to 18.1).
- The median PFS was 19.3 months (95% CI 14.8,-not reached).
- The 6-month and 12-month OS rates were 91% (95% CI 79%, 96%) and 79% (95% CI 65%, 88%), respectively. The median OS was not reached.

Quality of Life (QoL)

Patient-reported/QoL outcomes were not measured in the PROFILE 1001 trial.

Harm outcomes

As of 11-April-2014 data cut-off date, the median duration of treatment was 64.5 weeks (range 2.3 to 182.0).

- The most common AEs were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), an elevated aspartate aminotransferase level (22%), fatigue (20%), dysgeusia (18%), and dizziness (16%).
- The most frequently reported treatment-related grade 3 AEs included hypophosphatemia (10%), neutropenia (10%), and an elevated alanine aminotransferase level (4%). No grade 4 or 5 treatment-related AEs were reported.
- One patient (2%) discontinued crizotinib due to treatment-related nausea. Five patients died, all due to disease progression. The deaths were considered to be unrelated to the treatment

Ox Onc[4]

Ox Onc was a phase II, open label, single-arm study that enrolled East Asian patients with ROS1-positive advanced NSCLC who received ≤ 3 prior lines of systemic therapies. The trial was conducted in 37 sites in China, Japan, South Korea, and Taiwan. The primary endpoint of the Ox Onc trial was RECIST-defined ORR, as determined by Independent Radiology Review (IRR). Secondary endpoints included duration of response (DOR), time to first tumour response (TTR), disease control rate (DCR), PFS, and OS. Safety and patient-reported outcomes were also evaluated. . Crizotinib was administered orally at 250 mg twice daily in continuous 28-day cycles

until disease progression, unacceptable toxicities, or withdrawal from the study. Patients with disease progression could continue to receive crizotinib at the investigator's discretion

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

Efficacy

The key efficacy outcomes of the OX Onc trial are presented in Table 1.1.

As of 30-July-2016 data cut-off date, after median follow-up of 21.4 months:[2,3]

- ORR was 71.7% (95% CI 63.0%, 79.3%), including 17 (13.4%) patients with a complete response, 74 (58.3%) patients with a partial response, and 21 (16.5%) patients with stable disease. ORR results were not available for the subgroup of treatment-naïve patients.
- Disease control rate was 88.2 (95% CI 81.3, 93.2) at Week 8 and 80.3 (95% CI 72.3, 86.8) at Week 16 after initiation of crizotinib.
- The median TTR was 1.9 months (range 1.6 to 15.8), and the median DOR was 19.7 months (95% CI 14.1, not reached).
- The median PFS was 15.9 months (95%CI 12.9, 24.0),
- The median OS was 32.5 months (95% CI 32.5, not reached). The 6-month and 12-month OS rates were 92.0% (95% CI 85.7%, 95.6%) and 83.1% (95% CI 75.2%, 88.6%), respectively.

Quality of Life (QoL)

Patient-reported outcome results were reported over the first 20 cycles:

- Improvements in global QOL were statistically significant at cycles 3 to 5, 7, and 10.
- Clinically meaningful improvements (defined as ≥ 10 points change) were observed in patient-reported EORTC QLQC30 scores for insomnia, dyspnea symptoms at several time points.
- Clinically meaningful improvements were observed in EORTC QLQ-LC13 scores for patient-reported symptoms of cough and pain in chest, at several time points.
- A statistically significant and clinically meaningful deterioration from baseline was reported for constipations and diarrhea at multiple time points.
- Clinically meaningful improvements were observed in EORTC QLQ-LC13 scores for patient-reported symptoms of cough and pain in chest, at several time points.

Harm outcomes

As of 30-July-2016 data cut-off date, the median duration of crizotinib treatment was 18.4 months (range 0.1 to 34.1).

- Treatment-related AEs occurred in 96.1% of patients. The most frequently reported treatment-related AEs of any grade included elevated transaminases (55.1%), vision disorder (48.0%), nausea (40.9%), diarrhea (38.6%), and vomiting (32.3%).
- Grade 3 or 4 treatment-related AEs were reported in 25.2% of patients. The most common grade 3 or 4 treatment-related AEs were neutropenia (10.2%) and elevated transaminases (5.5%).

- 39 patients (30.7%) died during the study. Disease progression was the most common cause of death that occurred in 35 patients (27.6%). No crizotinib-related deaths were reported in the trial.

Table 1.1 : Highlights of Key Efficacy Outcomes in the PROFILE 1001 and Ox ONC trials

	PROFILE 1001 (N=53)	OX Onc (N=127)
Efficacy		
Primary Outcome,		
ORR, % (95% CI)	70 (56, 82)	72 (63, 79)
Key Secondary Outcome, median		
TTR median (range)	7.9 weeks (4.3, 32.0)	1.9 months (1.6, 15.8)
DOR[months], median (range)	17.6 (2.8, 18.1)	19.7 (14.1, NE)
PFS [months], median (95% CI)	19.3 (14.8, NE)	15.9 (12.9, 24.0)
OS		
OS [months], median (95% CI)	NE (NE, NE)	32.5 (32.5, NE)
6-month OS rate, % (95% CI)	91 (79, 96)	92 (86, 96)
12-month OS rate, % (95% CI)	79 (65, 88)	83 (75, 89)
CI = confidence interval, **HR** = hazard ratio; **NE**= not estimable; **NR** = not reported		

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Patient advocacy group input was provided by the Ontario Lung Association (OLA) and Lung Cancer Canada (LCC) on crizotinib as a single-agent for first-line treatment for patients with ROS1-positive advanced or metastatic NSCLC. Based on respondents' comments from LCC's submission, crizotinib provided patients with greater hope for a longer and better quality of life. Side effects of crizotinib were reported to be manageable, or patients reported being dose-reduced. The ability to take crizotinib as an oral pill was favoured compared to treatments involving injections at hospitals. Crizotinib also reduced the burden on caregivers, as there was a greater sense of independence among patients; patients were able to continue being employed, care for their families, and engage in physical activities. From the perspectives of patients with ROS1 positive NSCLC, they value a chance to extend their life and spend more time with their families by having a treatment that is effective, improves their symptoms and outcomes. They value the decreased toxicities and the manageable side effects allow them to a new normal with a high quality of life.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Guidance on treatment of multiple mutations (e.g., ROS1, EGFR, and ALK)
- Treatment sequence after progression on crizotinib first-line

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities

Registered Clinician Input

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

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

One report presenting data from an observational study was provided by the submitter. In the absence of comparative efficacy evidence, data from this study was used to inform the economic model. The Clinical Guidance panel also identified this study as being relevant.

EUROS1[5]

EUROS1was a retrospective study conducted in six European countries. The study included a consecutive series of patients who were identified to have a ROS1 rearrangement and treated with crizotinib (through an individual off-label use) in centres performing ROS1 testing. Data were collected retrospectively on patient and disease characteristics, lines of systemic therapies, type of chemotherapy or targeted therapy, and the date of initiation and end of treatment. Study endpoints included recurrence, survival events, best response rates (by RECIST version 1.1), and the occurrence of grade 4 or 5 toxicities.

A total of 32 patients were included in the study. All patients had stage IV progressive disease at the time of crizotinib treatment. The median age at diagnosis was of 50.5 years (range 34 to 78). Most patients were female (64.5%), never-smoker (71.0%), and had been diagnosed with a stage IV tumour (80.7%). All tumors were adenocarcinomas. All patients but one had received at least one prior line of treatment (97%). All patients had received crizotinib 250mg, twice daily, for a minimum duration of two weeks. Crizotinib was administered as a first- or second-line treatment in 32%, and as third or further lines of therapy in 68% of patients.

Efficacy

In the EUROS1 cohort, 80 % of patients achieved objective responses (16.7% with a complete response and 63.3% with a partial response); and the disease control rate was 86.6%. The median PFS time was reported to be 9.1 months, and the PFS rate at 12 months was 44%. At the time of analysis, 18 patients were still receiving treatment.

Quality of Life (QoL)

Patient-reported outcome were not reported in the EUROS1 study.

Harms Outcomes

Because this was a retrospective study, the authors of the study reports stated that monitoring safety outcomes was not possible in a prospective manner. Therefore, every investigator was asked to retrospectively declare all grade 4 and 5 AEs their patients reported while receiving crizotinib. According to Mazières et al., no unexpected AEs were observed in the EUROS1 study.

See Section 8 for more details.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for crizotinib in ROS1 positive NSCLC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Performance Status</td><td>The PROFILE 1001 trial limited eligibility to ECOG PS 0-2 and the OxOnc trial limited eligibility to ECOG PS 0-1.

PROFILE 1001[3]<table><tr><td>ECOG PS at Baseline</td><td>ROS1 cohort n (%)</td></tr><tr><td>0</td><td>23 (43.4)</td></tr><tr><td>1</td><td>29 (54.7)</td></tr><tr><td>2</td><td>1 (1.9)</td></tr></table>OxOnc[4]<table><tr><td>ECOG PS at Baseline</td><td>Total n (%)</td></tr><tr><td>0</td><td>34 (26.8)</td></tr><tr><td>1</td><td>93 (73.2)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP agree that the use of crizotinib in patients with an ECOG PS greater than 2 may be appropriate and should be left to the discretion of the treating oncologist.</td></tr>
<tr><td></td><td>Age</td><td>The median age of patients in the PROFILE 1001 ROS1 cohort was 55 years (range 25-81).[3]

The median age of patients in the OxOnc trial was 51.1 years (range 22.8 – 79.7).[4]</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>While the ROS1 mutation is more common in younger patients, the benefits of crizotinib in this population are generalizable to all patients regardless of the age.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Brain Metastases at Baseline	In the OxOnc study patients with brain metastases were eligible if asymptomatic or were neurologically stable for ≥2 weeks (if treated). A total of 121 out of 127 patients (18.1%) presented with brain metastases at the baseline.[4]	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The benefits of crizotinib in this population are generalizable to patients with stable brain metastases.
	Ethnicity or Demographics	All study participants were from Australia, South Korea and the United States cohort in the PROFILE 1001study. All study participants were Asian (58.3% from China, 20.5% from Japan, and the remaining 21.2% from South Korea and Taiwan) in the OxOnc Study.	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	The CGP agrees that the ethnicity of the study population is comparable to the Canadian population and therefore the results of the trials would be generalizable to the Canadian population.
	Biomarkers	In the Ox Onc trial, the ROS1 rearrangement was identified using apart fluorescence in situ hybridization (FISH) or a reverse-transcriptase–polymerase-chain reaction (RT-PCR) assay. In the PROFILE 1001 study, the ROS1 rearrangement was identified using FISH in the majority of patients (98%), and in one patient using RT-PCR († Based on the analysis of 50 patients)[1]	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)?	Routine testing for ROS1 through a validated test will be required in order to facilitate treatment decisions with crizotinib.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Intervention</td><td>Line of therapy</td><td>The reimbursement request is for first-line treatment for patients with ROS1-positive advanced NSCLC. However, the submitted trials included patients with previous treatment for advance disease. The majority of patients in both trials had at least 1 previous therapy for advance disease.

<u>PROFILE 1001</u>

<table>
<tr><td>Previous regimens for advance disease†</td><td>N (%)</td></tr>
<tr><td>0</td><td>7 (14)</td></tr>
<tr><td>1</td><td>21 (42)</td></tr>
<tr><td>>1</td><td>22 (44)</td></tr>
</table>
† Based on the primary analysis of 50 patients[1]

<u>OxOnx[4]</u>

<table>
<tr><td>Previous regiments for advance disease</td><td>N (%)</td></tr>
<tr><td>0</td><td>24 (18.9)</td></tr>
<tr><td>1</td><td>53 (41.7)</td></tr>
<tr><td>2</td><td>31 (24.2)</td></tr>
<tr><td>3</td><td>19 (15)</td></tr>
</table>
</td><td>Are the results of the trial generalizable to first line therapy?</td><td>The benefit of treatment with crizotinib is for all patients ROS1-positive advanced NSCLC regardless of line of therapy.</td></tr>
</table>

1.2.4 Interpretation

There were an estimated 28,600 new cases of lung cancer in Canada in 2017, and approximately 21,100 deaths from this disease making it the number 1 cause of cancer mortality in this country.[6] Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. Only about 30% of patients who present with Non-small Cell lung cancer present with resectable disease. Five year survival is only about 18% with little or no improvement over the last decade. Platinum based doublet chemotherapy has been the backbone of treating metastatic disease with small improvements in overall survival of about 2 months. Recent advances have identified driver mutations in NSCLC with kras mutations in 25%, EGFR in 15%, ALK gene rearrangements in 5% and ROS1 rearrangements in 1%. Targeted therapy has been shown to be clearly superior to chemotherapy in both the 1st and 2nd line setting. Crizotinib was approved by Health Canada in 2012 for ALK positive NSCLC patients, and in 2017 for ROS1 positive patients. ROS1 mutations are more common in adenocarcinomas, light or never smokers and younger patients.

Although ROS1 mutations could theoretically offer an improved prognosis, small studies of ROS1 mutation positive NSCLC patients treated with platinum based doublet chemotherapy shows that their survival is similar to patients without ROS1 mutations. Thus, there is an unmet need for need for new treatments in this population.

The PROFILE 1001 trial was a multicentre phase I dose escalation trial that was designed to assess the effectiveness of crizotinib 250 mg given twice daily in patients with ALK gene rearrangement positive NSCLC. The trial was amended to include patients with ROS1 gene translocations. A total of 53 eligible patients with ROS1-positive NSCLC were enrolled.

At the November 30, 2014 data cut-off date, with a median follow-up of 25.4 months, the overall response rate was 70% (95% CI 56, 82), including 5 patients with complete response (9.4%), 32(60.4%) with a partial response and 11 (20.8%) with stable disease. In the subgroup of 7 patients who had not received any prior therapy for metastatic disease the ORR was estimated to be 85.7% (95% CI 42.1, 99.6). The estimated median duration of response was 17.6 months (range; 2.8 to18.1); the median PFS was 19.3 months (95% CI 14.8, not reached). An updated analysis on June 30, 2018 demonstrated continued benefit, with a median duration of treatment of 22 months (95% CI: 15, 36), 12 patients (22.6%) remaining on treatment, and 26 deaths (49.1%) over a median follow-up period of 63 months. Median OS was 51 months (95% CI: 29, not reached) and the probabilities of survival at 12, 24 and 48 months were 78.8%, 67.0% and 50.7%, respectively. No new safety signals were noted.

Ox Onc was a phase II, open label, single-arm study that enrolled East Asian patients with ROS1positive advanced NSCLC who received ≤ 3 prior lines of systemic therapies. The trial was conducted in 37 sites in China, Japan, South Korea, and Taiwan. The primary endpoint of the Ox Onc trial was RECIST-defined ORR, as determined by Independent Radiology Review.

At the July 30, 2016 data cut-off date, with a median follow-up of 21.4 months, the ORR was 71.1% (95% CI 63.0%, 79.3%), including 17 (13.4%) patients with a complete response, 74 (58.3%) patients with a partial response, and 21 (16.5%) patients with stable disease. ORR results were not available for the subgroup of treatment-naïve patients.

Disease control rate was 88.2 (95% CI 81.3, 93.2) at week 8 and 80.3 (95% CI 72.3, 86.8) at week 16 after initiation of crizotinib. The median TTR was 1.9 months (range 1.6 to 15.8), and the median DOR was 19.7 months (95% CI 14.1, not reached).

The median PFS was 15.9 months (95%CI 12.9, 24.0). The median OS was 32.5 months (95% CI 32.5, not reached) and the 6-month and 12-month OS rates were 92.0% (95% CI 85.7%, 95.6%) and 83.1% (95% CI 75.2%, 88.6%), respectively.

Patient-reported outcomes were collected in the OxOnc trial. Improvements in global QOL were statistically significant at cycles 3 to 5, 7, and 10. Furthermore, clinically meaningful improvements (defined as ≥ 10 points change) were observed in patient-reported EORTC QLQC30 scores for insomnia, dyspnea symptoms at several time points. In addition, clinically meaningful improvements were observed in EORTC QLQ-LC13 scores for patient-reported symptoms of cough and pain in chest, at several time points. A statistically significant and clinically meaningful deterioration from baseline was reported for constipations and diarrhea at multiple time points.

Effectiveness: The two trials showed high response rates, durability of response and better than expected 6 and 12 month survivals than would be expected in this group had they been treated with platinum doublet chemotherapy: 30% 1 year survival with platinum based therapy and response rates of 15 – 30%, without receiving a ROS1 inhibitor. The median overall survival in metastatic NSCLC patients treated with platinum doublet chemotherapy is 9 to 11 months, with 30% of patients surviving to one year. Although crizotinib has shown high response rates and better than expected 1 year survivals in a phase I/II and phase II trial, the lack of a standard comparator arm limits the interpretation of progression free survival, overall survival and quality of life outcomes. It would be difficult if not impossible to do a randomized trial as the patient population is small, and there would be no equipoise if chemotherapy was chosen as a comparator.

Safety: Extensive experience with crizotinib in ALK mutated NSCLC has shown a good tolerability and improved quality of live in patients receiving ALK inhibitors as opposed to chemotherapy.[7] No new safety signals were seen in PROFILE 1001 or OxOnc trials. The most commonly reported treatment related grade 3 AEs in both trials were neutropenia and an elevated alanine aminotransferase level, which are manageable.

Burden of Illness: Of the 28,600 cases of lung cancer in Canada per year there are approximately 21,000 deaths. Non-small cell lung cancer accounts for about 13% of all lung cancer cases and NSCLC 87%.[6] As ROS1 mutations occur in 1 % of NSCLC there would be an estimated 250 new cases of ROS1 positive NSCLC per year. Some patients would present with early disease and be cured by surgery. A smaller minority would not be candidates for therapy, albeit as this mutation is more common in younger, non-smokers the co-morbidities would be expected to be less. The number of patients requiring treatment would likely be in the order of 220. As ROS1 mutation positive lung cancer is more common in younger, non-smoking patients the number of potential years of life lost would be expected to be greater.

Need: As chemotherapy has a marginal impact on median overall survival and ROS1 has been identified as a driver mutation in NSCLC there is a need for more effective therapies in this population. Target inhibition has led to improved outcomes in EGFR mutated and ALK gene rearrangements, and studies of crizotinib have shown high responses, along with durability and better than expected 1 year survivals. There is thus an unmet need in this population.

1.3 Conclusions

The Clinical Guidance Panel (CGP) believes there is a net clinical benefit for patients with ROS1 mutations receiving targeted therapy with crizotinib. This conclusion is based on two published single arm, phase I/phase II clinical trials of crizotinib with ROS1 positive NSCLC patients. The median OS is 51 months in the PROFILE 1001 trial and is 32.5 months in the Ox Onc trial. The overall response rates were clinically significant, above 70%, far exceeding response rates expected with platinum doublet chemotherapy. The durability of responses averaging around 17 months is also better than expected and one year survivals were over 80%, again better than the 30 to 40% expected 1 year survivals seen in platinum doublet chemotherapy. The quality of life scores were as expected in the previous crizotinib trials in ALK gene rearrangement NSCLC. The

safety profile of crizotinib appears favourable. The CGP thus agreed that there is a net clinical benefit of crizotinib in patients with ROS1 mutated NSCLC.

In making this conclusion, the CGP considered:

- The level of evidence in support of this conclusion is limited as there are no randomized trials evaluating crizotinib for ROS1 positive NSCLC patients. There would be no equipoise if chemotherapy was chosen as a comparator. Additionally, the small sample size of this patient population precludes the feasibility of conducting a randomized control trial. The CGP are not aware of any ongoing phase III confirmatory trials of crizotinib in patients with ROS1 positive NSCLC.

- The CGP notes that the reimbursement request is for crizotinib for first line treatment for patients with ROS1 positive NSCLC. The CGP agree that that the conclusion of a net clinical benefit of crizotinib is for patients with ROS1 mutations as the submitted pivotal trials demonstrate a favourable treatment effect in patients' naïve to treatment and in pretreated patients.

- An additional retrospective study (EUROS1) of 32 ROS1 positive patients with progressive disease at the time of crizotinib initiation, was submitted which demonstrated similar response rates to those observed in the two single arm phase I/II trials.

- The CGP notes that routine testing for ROS1 through a validated test will be required in order to facilitate treatment decisions with crizotinib. The CGP recognize that access to ROS1 testing may be a barrier to implementation because ROS1 testing is not currently part of standard of care.

- Driver mutations (ROS1, EGFR and ALK) are mutually exclusive. That is, the ROS1 mutation is exclusive of other oncogenic drivers and are considered non-overlapping. It is unlikely that patients will present with more than one mutation at the same time.

- Clinical trials and special access programs for targeted therapies, or platinum doublet chemotherapies or docetaxel could be options if disease progression occurs after failure on crizotinib. Patients with driver mutations, including the ROS1 mutation will likely not be considered for treatment with immunotherapy such as nivolumab or pembrolizumab in the post-progression setting as they are not likely to respond to this type of therapy.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

There were an estimated 28,600 new cases of lung cancer in Canada in 2017, and approximately 21,100 deaths from this disease making it the number one cause of cancer mortality in this country.[6] Non-small cell lung cancer accounts for about 85% of all lung cancer cases. Only about 30% of patients who present with Non-small Cell lung cancer present with resectable disease. Five year survival is only about 18% with little or no improvement over the last decade. Platinum based doublet chemotherapy has been the backbone of treating metastatic disease with small improvements in overall survival of about 2 months. Recent advances have identified driver mutations in NSCLC with kras mutations in 25%, EGFR in 15%, ALK gene rearrangements in 5% and ROS1 rearrangements in 1%. Targeted therapy has been shown to be clearly superior to chemotherapy in both the first and second line setting.

Crizotinib was approved by Health Canada in 2012 for ALK positive NSCLC patients, and in 2017 for ROS1 positive patients. ROS1 mutations are more common in adenocarcinomas, light or never smokers and younger patients. The ROS1 mutation is felt to be mutually exclusive of ALK, EGFR and KRAS mutations, and occur in approximately 1% of lung cancers.[8]

2.2 Accepted Clinical Practice

As chemotherapy has a marginal impact on median overall survival and ROS1 has been identified as a driver mutation in NSCLC there is a need for more effective therapies in this population. Target inhibition has led to improved outcomes in EGFR mutated and ALK gene rearrangements, and studies of crizotinib have shown high responses, along with durability and better than expected 1 year survivals. There is thus an unmet need in this population.

Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, is the available and funded first-line therapy for metastatic ALK-positive NSCLC in Canada. This is based on an open label phase III study that confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and progression-free survival (PFS) [median 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001)] favouring crizotinib when compared to first-line platinum doublet chemotherapy; overall survival was not different between the two arms, likely due to the high rate of cross-over to crizotinib in the chemotherapy arm.[7] Crizotinib is continued in the absence of disease progression or unacceptable toxicity, and may be continued past radiologic progression particularly if progression occurs only in limited sites of disease and is controlled with other modalities, or if the patient is continuing to derive clinical benefit in the prevention of symptoms and maintenance of quality of life. In the PROFILE 1014 trial, 73% of patients were treated beyond radiologic progression with crizotinib, for a median of 3.1 months. However, patient impactful disease progression on crizotinib inevitably occurs in the majority of patients usually within 12 months. This may be due to development of ALK resistance mutations, gain in copy number, or alternative signaling pathways.[9] Most commonly, disease progresses in the Central Nervous System (CNS), as not only is the penetration of crizotinib low into the CNS, but ALK positive disease has a predilection for CNS spread. If CNS is the only site of progression, and disease outside the

CNS is controlled with crizotinib, then local therapy with radiation is often used to treat the site(s) of progression and crizotinib is continued. This temporarily halts progression in the CNS, but it inevitably grows again in this area.

The activity of check-point inhibitors (immunotherapy) is largely unknown as very few patients with driver mutations were included in the check-point inhibitor clinical trials. In first line immunotherapy clinical trials, ALK, ROS, and EGFR positive patients were specifically excluded. Although there were some of these patients in second line trials, the durable clinical benefit rate for immunotherapy is quite low in low mutation burden tumours. Oncogenic dominant driver mutation cancers – such as ALK positive and ROS1 positive lung cancers – fit this group of poor responders to immunotherapy. The paradigm for the management of patients with dominant treatable oncogenic mutations is to treat with all active TKI's first before considering chemotherapy, with immunotherapy most often reserved for progression after chemotherapy options are exhausted.

2.3 Evidence-Based Considerations for a Funding Population

The PROFILE 1001 trial was a multicentre phase I dose escalation trial that was designed to assess the effectiveness of crizotinib 250 mg given twice daily in patients with ALK gene rearrangement positive NSCLC. The trial was amended to include patients with ROS1 gene translocations. A total of 53 eligible patients with ROS1-positive NSCLC were enrolled. In this study, crizotinib demonstrated marked antitumor activity in patients with advanced ROS1- rearranged NSCLC.[1]

2.4 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, and RON. 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.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient advocacy group input was provided by the Ontario Lung Association (OLA) and Lung Cancer Canada (LCC) on crizotinib as a single-agent for first-line treatment for patients with ROS1-positive advanced or metastatic NSCLC, and their input is summarized below.

OLA obtained feedback from a Toronto based lung health support group which composed of six members, including one patient with lung cancer, one with idiopathic pulmonary fibrosis (IPF), and four with chronic obstructive pulmonary disease (COPD). OLA also conduced one phone interview with a patient with lung cancer. Input from the lung health support group and the phone interview were obtained during September 2018. OLA also incorporated previous feedback they had submitted to CADTH over the past three years within this submission. All information was obtained from Canadian respondents. Input from a certified respiratory educator (CRE) was also incorporated by OLA as a way to enhance their patient input submission. OLA stated that the CRE was used as a *"review check,"* where the CRE reviewed the submission and offered feedback and suggestions as appropriate. None of the respondents included in OLA's submission reported experience with crizotinib.

LCC conducted individual interviews and an environmental scan of online forums for patients with ROS1-positive NSCLC. LCC also conducted a survey of patients with ROS1-positive NSCLC. All data were gathered between August and November 2018. In total, LCC incorporated the feedback of 30 patients and 11 caregivers, of whom 33 were female and eight were male (see Table 3.1).

Table 3.1: Breakdown of Respondents from Lung Cancer Canada

Input Source	Gender, n		Caregiver/patient, n		Country Source
	Male	Female	Caregiver	Patient	
Environmental Scan, n=5	1	4	2	3	N/A
Individual Interviews, n=6	1	5	0	6	Canada, n=2 USA, n=2 Belgium, n=1 Netherlands, n=1
Survey responses, n=30	6	24	9	21	Canada, n=2 USA, n=18 Netherlands, n=1 Germany, n=2 China, n=7
Faces of Lung Cancer Survey (2015)	NR	NR	72	91	NR
Abbreviations: NR=Not reported by LCC					

LCC stated that the ROS1 mutation has been found to be more common among women and non-smokers. The national Faces of Lung Cancer Survey (FLCS) conducted by LCC in August 2015 was completed by 91 lung cancer patients and 72 caregivers who were, at the time, currently caring for or had previously cared for patients living with lung cancer; LCC included information gathered from this survey into their submission as well. A total of 41 respondents in LCC's submission reported experience with crizotinib, of whom 22 received it in the first-line, 12 in the second-line and seven who did not report this information.

Sentiments regarding the lack of timeliness in getting diagnosed were made by patients from both OLA and LCC's submissions; the delays in diagnosis resulted in increased anxiety for patient and their families. Symptoms of lung cancer were described as debilitating and significantly impacting the day-to-day living of patients. Overall, patients and caregivers expressed a need for more information at diagnosis about their condition in terms that are understandable to them, and greater time and appreciation from their doctors, as they expressed feeling rushed during appointments. Current standard of care was reported to be chemotherapy. Patients reported feeling burdened by their many hospital visits due to chemotherapy, and that side effects significantly impacted their lives.

Based on respondents' comments from LCC's submission, crizotinib provided patients with greater hope for a longer and better quality of life. Side effects of crizotinib were reported to be manageable, or patients reported being dose-reduced. One patient had to stop crizotinib due to side effects, however commented that they would still support the use of crizotinib, as it allowed them to continue working and spend quality time with their family. The ability to take crizotinib as an oral pill was viewed preferentially compared to treatments involving injections at hospitals. Crizotinib also reduced the burden on caregivers, as there was a greater sense of independence among patients; patients were able to continue being employed, care for their families, and engage in physical activities. From the perspectives of patients with ROS1 positive NSCLC, they value a chance to extend their life and spend more time with their families by having a treatment that is effective, improves their symptoms and outcomes. They value the decreased toxicities and the manageable side effects allow them to a new normal with a high quality of life.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

Both OLA and LCC indicated the stress that patients feel due to their diagnosis of lung cancer. OLA commented on increased levels of patient anxiety arising from issues around timeliness of their diagnosis. OLA provided the following quotes that highlight the delay patients and caregivers experience in waiting for a diagnosis, and the stress that it results in:

"I waited many months to see a specialist not knowing what exactly was wrong with me or what the prognosis might be." - Female patient

"It took a year to finally make the diagnosis." - Female patient

"The most frustrating thing for me was how long it took to get her diagnosed." - Daughter of lung cancer patient

Pain, which could be very intense at times, shortness of breath, cough, weakness and extreme fatigue or exhaustion were mentioned by OLA to be symptoms of lung cancer experienced by patients. Symptoms were mentioned to be inconsistent and changing frequently making them difficult for patients to manage. Extreme fatigue was mentioned specifically as being difficult for patients to handle by OLA, as patients were mentioned to have to plan their days around managing their exhaustion.

OLA emphasized the impact symptoms of lung cancer can have on the day-to-day lives of those living with it, including the ability to work, travel, socialize and participate in leisure and physical activities. Symptoms were also mentioned to impact patient's relationships with family and friends, their emotional well-being and their financial situation. OLA highlighted the impact lung cancer can have on a patient's sense of independence, as one patient stated that *"it robbed me of my ability to do anything on my own."* Another patient commented specifically on how lung cancer impedes them from partaking in daily tasks, and how they have had to adjust to be dependent on others: *"this disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must use volunteer drivers to get to my appointments. I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful."*

OLA stated that interviewed respondents felt a need to be better informed and for greater help to navigate their condition and the decision-making process. Respondents were reported to have felt that they needed greater information about cancer in general or lung cancer specifically, treatment options, and the eventual prognosis in terms that would apply to them. OLA mentioned that several individuals indicated feeling rushed at appointments with doctors, and would have preferred to receive information in digestible, *"easy to understand"* language with clear thoughts about treatment choices and prognoses.

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

OLA included the following list of treatments that interviewed patients reported using: Spiriva, Seebri, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza, and Ventolin (as needed); one patient was reported to be treated with chemotherapy, and another had received a lung transplant in early 2018. OLA stated that patients thought current treatments helped to provide relief for some symptoms such as fatigue, shortness of breath, cough, appetite loss and low energy. However, other symptoms, including palpitations, dry mouth, mouth sores, vision and urinary problems, and impact on mood were stated as needing better management. In particular, radiation therapy

LCC stated that the current standard therapy for patients with NSCLC is intravenous chemotherapy and radiation therapy and/or immunotherapy. Side effects of chemotherapy and radiation therapy were mentioned by LCC to impede patient's engagement in daily activities. Radiation therapy was mentioned by OLA to leave a patient with an extremely sore and painful throat, making swallowing food very difficult. Another patient was also reported by LCC to have experienced hair loss, neutropenia and difficulty swallowing which resulted in them being put on a liquid diet; this patient then developed peripheral neuropathy, and described their experience of their second round of chemotherapy as feeling like she had the flu all the time and that she lost her voice.

LCC mentioned that patients experienced nausea, vomiting and extreme fatigue while on chemotherapy. OLA also noted the fatigue experienced by patients due to treatments, and their desire for increased energy. A weakened immune system was another symptom of chemotherapy and radiation therapy experienced by patients, as reported by LCC. Due to chemoradiation, one patient's white and red blood cells were depleted, making her unable to go out or have visitors. A patient who was also a mother described being unable to spend time with her children or be involved in their daily activities. LCC emphasized the impact of both lung cancer and treatment on family life, as it was stated that ROS1-

positive NSCLC patients tend to be female and younger than the average lung cancer patient, making it more likely that these patients will have dependent children to take care of.

While side effects of chemoradiation therapy are experienced by patients, LCC stated that many patients had their cancer controlled by receiving a curative dose of chemoradiation. However, with time patients did experience progression after treatment. One patient reported experiencing progression form stage 3 to stage 4 while on treatment. Treatment also resulted in what LCC described as "chemo fog," which involved having to deal with distractibility, and issues with memory and word-finding. For the two patients who experienced "chemo fog," these symptoms greatly impacted their ability to work; one of the patients, who was a professor, had to quit their job, while the other, who was retired, found that their life seemed to revolve around their treatments. LCC indicated that impacts on work that result in reduced productivity or having to quit can lead to financial difficulty for patients and their families.

Both OLA and LCC commented on the frequent number of hospital visits required for treatments and the inconveniences as a result of them. OLA highlighted the cost burden associated with the numerous hospital visits, as one patient reported having to use an out-of-pocket service to drive them to and from their treatment appointments. Other secondary costs were also mentioned, such as having to purchase certain foods to maintain good nutrition and counter experienced weight loss; for senior patients with fixed incomes or pensions, these added costs can place an additional burden on top of their disease experience.

OLA mentioned that patients hoped for treatments that would allow them to require less assistance from others, and retain their sense of independence. LCC stated that patients who underwent treatment with immunotherapy experienced fewer side effects and felt better in a shorter time after receiving treatment, compared to patients who were treated with chemotherapy. Side effects of immunotherapy were listed to be nausea, fatigue and diarrhea. LCC also stated that while the studies indicate that immunotherapy may provide lung cancer patients with better quality of life, it may not be as effective for ROS1-positive patients.

None of the respondents interviewed by OLA, even patients with advanced disease, considered the idea of not being treated. Rather, respondents seemed to be interested in being better informed about understanding their treatment options and what these options may mean for them. Clearer communication about treatment options and their implications for the disease experience was stated as being imperative for patient's decision making processes and coping. OLA also suggested that training be provided for general practitioners to address patient's concerns about delays in being diagnosed and treated.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

OLA and LCC indicated that caregivers of lung cancer patients experience negative impacts to their lives similar to the patients themselves. Similar to the impact of lung cancer on patients, caring for loved ones was reported to impact the finances, work, relationships with friends and family, and physical and leisure activities of caregivers. Based on the FOLCR survey, over half of caregivers (59%) reported a reduced number of hours worked, and 8% reported having to quit their jobs. Caregivers also noted an impact on their independence and their ability to travel and socialize. OLA also mentioned the emotional toll caregivers experience by watching their loved ones suffer, knowing there is little they can do to ease their discomfort and pain. LCC stated that caregivers may feel additional

burden and isolation due to subconscious attitudes and negative implications regarding lung cancer. Caregivers were mentioned to experience anxiety, worry, depression, and psychological distress resulting and decreased quality of life due to feeling the need to take "ownership for protecting their loved ones."

LCC indicated that caregivers need to juggle many roles at once, as they take care of needs at home, at their jobs, and as caregivers while incorporating the many appointments their loved ones must attend. One patient described the difficulty her family had in accepting her diagnosis and adjusting to their new reality; she mentioned that her family has since accepted her diagnosis, and that she and her sister can laugh about it now. One patient described her diagnosis as being a very depressing time for her family, while another patient's wife became depressed and began receiving medication to treat her depression as a result of his diagnosis.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Crizotinib

None of the patients in the OLA's evidence group reported having experience with crizotinib. All information regarding experiences with crizotinib in this section are reported on behalf of respondents of LCC's submission. LCC provided a chart summarizing patient reported outcomes regarding crizotinib. A total of 41 respondents were included as having reported experience with crizotinib, the majority (n=33/41, 81%) of whom were female with an average of 55 years of age, although two patients did not report their age. Eleven respondents were caregivers who provided information on behalf of patients, while the remaining information was provided by patients. A total of 22 patients reported receiving crizotinib as first-line therapy, 12 reported receiving it in the second-line, and seven did not report this information.

Fifteen patients experienced a reduction in tumour or nodule size or in number of tumours. Ten patients experienced stable disease. Six patients reported no evidence of disease (NED); one of these patients was NED for five years until she experienced progression; another was NED for seven months before chemotherapy was added to their regimen. Two patients reported having a complete response; one patient reported feeling better; and another patient's status was unknown as they had just started receiving crizotinib. Five patients reported progression, however, one of these patients had a response for ten months before progression occurred.

LCC also compared patient's duration of response to the median PFS of 9.1 months observed in a pivotal trial of crizotinib for ROS1 positive NSCLC. Twenty-seven patients who reported using crizotinib had a duration of response greater than 9.1 months. Fourteen patients had a duration of response less than 9.1 months, nine of whom started receiving crizotinib in 2018 and are still on crizotinib. Nine patients were no longer receiving crizotinib, while 27 patients were still receiving crizotinib. One of the patients receiving crizotinib also had carboplatin and pemetrexed added to their regimen in 2018.

LCC stated that in many cases, the responses of the patients included in their input far exceeded the trial results and expectations of survivorship for a lung cancer population. Based on the data provided by LCC, crizotinib may bolster a patient's sense of hope, and chance for a longer and better quality of life.

LCC reported the numerous benefits experienced by patients. One patient progressed following chemoradiation and was then given crizotinib which resulted in being NED for almost three years. Another patient was NED for five years while on crizotinib and is reportedly doing well. Crizotinib was considered a life saver for a patient who received crizotinib for 68 months and is now NED. By six months, the lung tumour of another patient was nearly gone, and her lymph node metastasis disappeared within three months; this patient was able to celebrate her third cancerversary. One patient was given a prognosis three to eight months when he was diagnosed, however he has been NED for three years now and stated, *"This has enabled me to live a normal life which included seeing the birth of two grandkids, travel and many rounds of gold with my wife and friends. I hope to be on this drug for many more years."*

When asked about side effects related to crizotinib, most patients said that side effects were manageable. For some patients, management of side effects meant a dose reduction. Edema experienced by one patient resulted in a dose reduction from 250mg to 200mg of crizotinib. Two other patients also reported a dose reduction as a result of side effects. One patient had to stop receiving crizotinib because her liver enzymes did not normalize even after dose reduction; however, this patient still supported the use of crizotinib for treatment of her lung cancer stating, *"despite the experiences I had in dose reduction and finally termination, I still would have chosen to go on crizotinib again instead of chemotherapy. While on crizotinib, I was able to keep working full time to support my family. It gave me 6 moths to then qualify to participate in a Phase 1 trial.."* Table 3.2 reports the side effects reported by patients while they were receiving crizotinib. Visual issues, diarrhea, edema and nausea were the most common side effects reported.

Table 3.2: Side effects experienced by patients due to crizotinib

Side Effects	**No of Patients**
Visual Issues	13
Diarrhea	13
Edema	11
Nausea	8
Fatigue	5
Acid Reflux	4
Taste Changes	4
Constipation	4
Dizziness	3
Elevated Liver Enzymes	3
Vomiting	3
Decreased WBC	2
Decreased Testosterone	1
Low Platelets	1

Patients who received crizotinib in the first line (n=22) found their side effects were manageable, and that they were able to take on day to day activities and engage in a

normal life. Twelve patients reported receiving crizotinib as second-line therapy following chemoradiation; these patients expressed feeling much better on crizotinib compared to chemoradiation. Efficacy, convenience, manageable side effects, and remaining progression free were listed as patient's expectations for crizotinib.

As crizotinib is administered twice a day and orally, allowing patients to take their treatment while at home, and reducing the need for injections and long hospital visits or stays. Patients reported feeling less tired after treatment and were able to go to appointments on their own. The reduced dependence on others helped to alleviate the burden of lung cancer on both the patients and caregivers. Patients reported being able to stay active and achieve new things. Patients reported being able to engage in exercise, cooking, and other activities including fishing, swimming, biking, walking, driving and caring for their families. One patient stated feeling a new sense of purpose through advocacy and helping to make a difference in the lives of other lung cancer patients. One patient had lost 25lbs, struggled with breathing and was on oxygen before crizotinib; after crizotinib this patient's status improved with her stating, "Most days there is very little to remind me that I have lung cancer except for taking my medication twice daily." Another patient commented saying, "It is as if I do not have lung cancer."

Patients and their families feel a greater sense ease as a result of crizotinib, giving them a greater sense of hope. LCC stated that patients were able to achieve close-to-normal standards of living with very high levels of functioning. As a result of treatment, many patients were able to return to work. Patients reported being able to return to their jobs either in a full-time or part-time capacity as teachers, lawyers, or professors. Two patients reported starting new jobs as patient advocates. Returning to work helps patients reduce the financial burden placed upon them and their families as a result of their lung cancer.

3.3 Companion Diagnostic Testing

LCC indicated that tissue based sampling must occur for detection of ROS1. Tissue sampling may pose barriers for some patients, including having inadequate tissue sample for testing, and time required for testing. LCC advocates that there is a need for more efficient and less invasive testing procedures. Testing patients for ROS1 status should not be a barrier to treatment, and LCC posits that next generation panel testing and blood based tests should be explored in order to truly provide personalized medicine.

3.4 Additional Information

LCC provided a quote from a patient which highlighted the goal for all patients to achieve functional status and good quality of life: "Although a difficult journey, thanks to crizotinib, I am still able to have a functional and fulfilling lifestyle." LCC recognized that Canada is a country that allows patients to access treatments that are publicly funded, allowing patients to access treatments they might not otherwise be able to afford. However, they assert that Canadian HTA processes have not kept pace with the advancing treatment paradigms. LCC insists that phase 2 data should not be a barrier to access for patients. As molecular targeted therapies and research become more customized to specific subsets of patients, LCC points out that sample sizes will continue to decrease which will increase the difficulty in conducting phase 3 trials. The UK's Cancer Drug Fund was include as an example of how to manage processes regarding more customized treatments for smaller groups of patients, as they evaluate under the processes of orphan or rare diseases; Canada does not have a similar process to this, however LCC states that

Canada should explore and support global collaborations and registries to collect real world evidence and patient reported outcomes.

LCC provided a statement endorsing the use of crizotinib for ROS1-positive patients on behalf of both patients and physicians. LCC provided a letter from The ROS1ders, a group consisting of 259 patients and caregivers with ROS1-positive NSCLC from 32 countries. The letter from the ROS1ders states that crizotinib is more effective at treating ROS1-positive NSCLC, and allows patients to experience better quality of life. Rather than living with a terminal illness, the ROS1ders state that crizotinib allows for patients to live with a chronic illness; a disease that will one day be fatal, but that no longer puts them at an *"end of life"* state. The letter highlighted that many patients diagnosed with ROS1-positive NSCLC are younger than typical lung cancer patients with families to take care of, and that treatment with crizotinib has allowed them to continue being employed and taking care of their familial responsibilities. The letter further states that conducting a phase three randomized controlled trial to further prove the efficacy of crizotinib might be unethical, as known comparator treatments, such as chemotherapy, are shown to be less effective than crizotinib, and that the sample frame of patients with ROS-1 positive NSCLC is too small. The International Association for the Study of Lung Cancer (IASLC), the College of American Pathologists (CAP), and the Association for Molecular Pathology (AMP) were stated to strongly recommend testing for ROS1 in the 2018 update to their lung cancer molecular testing guidelines. Overall, the letter urged HTA bodies to provide crizotinib as a treatment option for ROS1-positive NSCLC patients.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Guidance on treatment of multiple mutations (e.g., ROS1, EGFR, and ALK)
- Treatment sequence after progression on crizotinib first-line

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities

4.1 Currently Funded Treatments

PAG noted that the standard of care for patients with ROS1 mutation positive NSCLC is chemotherapy (e.g., cisplatin plus pemetrexed). Patients could also receive an ALK inhibitor (e.g., crizotinib) or pembrolizumab.

4.2 Eligible Patient Population

There are several possible mutations in the advanced NSCLC setting (e.g., ROS1, EGFR, and ALK). PAG is seeking confirmation that these mutations are mutually exclusive and guidance on how patients with more than one treatment would be treated (i.e., which mutation would clinicians treat first).

Crizotinib is associated with poor CNS penetration, PAG is seeking guidance on whether patients with ROS1 mutation positive advanced NSCLC who have CNS involvement would be eligible for treatment with crizotinib.

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients with ROS1 positive NSCLC who are currently receiving first-line chemotherapy
- Patients with ROS1 positive NSCLC who have previously been treated with chemotherapy and/or PD-1 inhibitor (e.g., nivolumab, pembrolizumab)

4.3 Implementation Factors

As there would only be a small subset of patients who were ROS1 positive, the overall numbers of patients accessing crizotinib is likely to be small. This is an enabler to implementation.

The dose of crizotinib is well-known as crizotinib is a standard of care for first-line ALK positive NSCLC. As crizotinib is administered orally, PAG identified that chemotherapy units and chair time would not be required. In addition, health care professionals are familiar with the administration and monitoring of crizotinib. These are enablers to

implementation.

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

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

PAG also noted that additional health care resources may be required to monitor and treat toxicities, in particular, cardiac (e.g., QT prolongation, bradycardia) and ocular toxicities.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on treatment sequencing with chemotherapy, PD-1 or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab). PAG is seeking confirmation whether the same treatment algorithm for crizotinib in ALK positive patients would apply for ROS1 positive patients.

For ROS1 positive patients who have received crizotinib in the first-line setting, PAG is seeking whether second-line treatment with an ALK inhibitor (e.g., ceritinib, alectinib) would be an option. PAG is also seeking clarity on whether ALK inhibitors can be used interchangeably for patients with a ROS1 mutation and preference for an ALK inhibitor.

4.5 Companion Diagnostic Testing

PAG noted that ROS1 is not routinely available in all provinces. PAG members noted there is no formalized testing process or funding in place for ROS1 in jurisdictions. Health care resources and coordination to conduct the ROS1 testing in the first-line setting will be required. The significant increase in costs for ROS1 testing is a barrier to implementation.

PAG had concerns related to:

- the turnaround time for ROS1 testing
- whether all NSCLC patients are required to be tested for ROS1
- how testing is performed (i.e., through IHC or FISH or other methods)
- as patients are currently tested for EGFR, PD-L1, and ALK in the first-line setting, whether there will enough tissue sample to test for ROS1 as the fourth test

Therefore, the number of patients requiring ROS1 testing and access to ROS1 testing may be a barrier to implementation.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

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

In response to implementation questions, the clinicians noted that ROS1 and ALK share similar homology, however, treatments for these targets should not be used interchangeably. Some drugs that target ALK, such as lorlatinib and ceritinib, were stated to have shown efficacy in treating ROS1. However, other effective ALK inhibitors, such as alectinib, do not show the same efficacy when treating ROS1. Testing for ROS1 currently occurs via fluorescence in situ hybridization (FISH), however it is expected that testing will predominantly be via immunohistochemistry (IHC) testing in the future. Testing for ROS1 is expected to increase in the future, and the clinicians noted that provincial funding plans/algorithms should incorporate this alongside EGFR and ALK testing.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for ROS1 Positive NSCLC

The clinicians indicated that chemotherapy, typically platinum-based chemotherapy plus pemetrexed, is the standard of care for patients with ROS1-positive NSCLC. Compared to effective targeted therapies, the input suggested that the benefits of chemotherapy are modest.

Other standard treatment options are immunotherapy, including nivolumab or pembrolizumab. The clinicians indicated that while crizotinib is not publically funded in Canada, patients may currently access crizotinib through special access programs in some provinces.

5.2 Eligible Patient Population

The clinicians noted that oncogenic drivers, such as KRAS, EGFR or ALK, in NSCLC are mutually exclusive, and that patients with the ROS1 molecular subset are expected to compose approximately 1% of NSCLC patients. The clinicians suggested that all patients with the ROS1 rearrangement would be candidates for treatment with crizotinib due to the higher rates of objective response, durable responses, and improvement in progression free survival compared to treatment with standard available therapies.

The clinicians also noted the available evidence supporting the use of crizotinib in ROS1 positive NSCLC patients included fairly robust and consistent data from phase II trials and real world studies. They acknowledged that conducting a phase III randomized study of crizotinib versus chemotherapy would be unethical and, hence, unlikely in this setting. The collection of real world data currently ongoing by other groups helps support the efficacy of crizotinib among ROS1 patients. In addition, the input stated that Canadian clinicians have started preliminary

discussions on the possibility of developing a lung cancer registry to capture important real world evidence.

5.3 Relevance to Clinical Practice

The clinicians highlighted that, until recently, ROS1 testing for patients was difficult to obtain through Canadian pathology labs. Identification of patients with the ROS1 rearrangement was considered opportunistic, as patients who were young and never smokers were mostly targeted for testing. The group of clinicians who submitted input indicated having treated a total of 13 ROS1 patients previously with crizotinib; the clinicians described their patients as being similar to patients identified in studies (young never smoking individuals). Therefore, the clinicians suggested that their "real world experience" in treating patients with ROS1 rearrangement is similar to what has been reported in studies; they found that responses typically seen were durable, and patients' wellbeing and quality of life improved. The clinicians suggested that as the population of patients with ROS1 rearrangement are typically younger, treatment with crizotinib can be associated with the ability for these patients to return to work or family responsibilities.

The clinicians listed chemotherapy with a platinum-based doublet and immunotherapy as the main treatment options for the patient population of interest. Compared to chemotherapy, the clinicians reported that targeted therapies are better tolerated and more positively impact patient's quality of life. However, due to the rare nature of ROS1, it was stated that there were no large datasets on outcomes with immunotherapy. Considering ROS1 together with other oncogene driven cancers that are predominantly seen in never smokers, the clinicians felt that the response rates to immunotherapy tend to be lower and the duration of responses are shorter than for the general population. In addition, crizotinib was suggested to be a well-tolerated drug. Clinicians reported feeling confident in managing side effects that may occur with crizotinib due to their experience with using it for ALK-positive patients.

Considering the above-mentioned facts, the clinicians providing input suggested targeted therapy with crizotinib as the preferred first-line option for ROS1 positive patients.

5.4 Sequencing and Priority of Treatments with Crizotinib

The clinicians providing input noted that patients with ROS1 rearrangements would follow a very similar algorithm to ALK positive patients. They felt a ROS1-directed therapy would be the best upfront treatment option. Therefore, if ROS1 status is known before initiation of therapy, the clinicians stated crizotinib would be the first line treatment (which is in agreement with currently available guidelines); and next generation inhibitors (e.g., lorlatinib) would likely be used after crizotinib. Patients who progress on ROS1-directed therapy would then move on to chemotherapy, typically with a platinum and pemetrexed doublet. If ROS1 rearrangement is discovered during or after first-line systemic therapy, crizotinib would be given as second-line therapy.

According to the clinicians, due to the rare nature of ROS1 positivity, data for the effectiveness of immunotherapy in this small population was not available. However, similar to other oncogene-driven cancers that occur in never smokers (e.g., EGFR and ALK), immunotherapy with PD-1/PD-L1 inhibitors would be typically reserved for the later lines of therapy, given lower response rates when compared to a smoking population.

5.5 Companion Diagnostic Testing

ROS1 rearrangement was stated to be originally detected by fluorescence in situ hybridization (FISH) with a ROS1 break apart probe. However, FISH was also stated to be technically demanding and costly, preventing uniform implementation of ROS1 testing across Canada. Currently, the Canadian ROS (CROS) initiative, which is ongoing in 14 centres across Canada, aims to validate immunohistochemistry (IHC) testing for ROS1 translocations in NSCLC tumour samples. Routine IHC testing for ROS1 has not been uniformly implemented across the country. Once it is conducted routinely, testing for patients with newly diagnosed adenocarcinoma should be widely available. Advantageously, ROS1 can be added as a standard biomarker panel for patients using IHC, similar to testing for ALK and PD-L1.

In addition to FISH and IHC, other techniques to detect ROS1 translocations were stated to be next generation sequencing (NGS) of RNA and DNA, and polymerase chain reaction (PCR). The clinicians recognized that technologies for biomarker testing and the capabilities of different provincial labs are rapidly changing; therefore, they proposed the use of any validated test to detect ROS1 rearrangement, with IHC expected to be the predominant test at this time. It was noted that the American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and International Association for the Study of Lung Cancer (IASLC) 2018 guidelines recommend that all adenocarcinoma patients be tested for ROS1 along with EGFR and ALK. Canadian guidelines also recommend that all patients with advanced non-squamous NSCLC be tested for ROS1 rearrangement at diagnosis, clinicians indicated that this testing should be incorporated in provincial algorithms.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 In regards to question 3.4 above, please consider the optimal sequencing following treatment with crizotinib, specifically: chemotherapy, PD-1, or PD-L1 inhibitors (e.g., nivolumab, pembrolizumab, atezolizumab). In addition, whether the same treatment algorithm for crizotinib in ALK positive patients apply for ROS1 positive patients.

See section 5.4.

5.7.2 In clinical practice, how are patients currently being tested for ROS1 mutations? If crizotinib was reimbursed for patients with ROS1 mutations in this setting, how would the current practice for the testing for ROS1 mutations change?

See section 5.5.

5.7.3 Please comment on whether ROS1, EGFR, and ALK mutations are mutually exclusive. Can a patient present with more than one mutation? If yes, which mutation would you treat first? Can a patient develop a mutation to either ALK, EGFR, or ROS1 over time? If yes, how are these patients clinically managed?

ROS1 was stated to almost always be exclusive of other oncogenic drivers, therefore the concern regarding which oncogenic driver to treat first is something rarely seen in clinical practice. As with other oncogene driven cancers, it is expected that patients

will eventually develop resistance to ROS1 therapy. Currently, the molecular underpinnings of resistance to ROS1 directed therapy are being studied; to overcome resistance to crizotinib, the use of other ROS1 inhibitors may be considered in the future.

5.7.4 In clinical practice, can ALK inhibitors be used interchangeably for patients with a ROS1 mutation? If yes, what is the preferred ALK inhibitor? Please comment on the preference considering patient preference, efficacy, safety, and administration.

ROS1 rearrangement shares homology with ALK, as these patients share similar adenocarcinoma histology, histomorphology, are often of young age, and a high prevalence of non-smoker status. While ROS1 shares significant homology with the ALK kinase domain, it is not identical to ALK, which eliminates the option of using drugs for these indicators interchangeably. Some drugs that target ALK, such as lorlatinib and ceritinib, were stated to have shown efficacy in treating ROS1. However, other effective ALK inhibitors, such as alectinib, do not show the same efficacy treating ROS1.

The clinicians stated that current data supports the use of crizotinib for ROS1 driven NSCLC. Lorlatinib was also stated to show activity among ROS1 patients; loratinib has not yet been approved by Health Canada, it has recently received approval from the FDA for ALK patients. Certinib also shows activity among ROS1 patients, with uptake to date limited by dosing and side effect considerations.

6 SYSTEMATIC REVIEW

6.1 Objectives

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

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 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team is provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of crizotinib for ROS1 positive NSCLC will be included.	Adult patients with histologically or cytologically verified locally advanced or metastatic NSCLC positive for ROS1 rearrangements not amenable to curative therapy (first-line setting). <u>Subgroups:</u> – Age group (≤65 years vs. >65 years) – Sex (male vs. female) – Baseline ECOG performance status (0 vs.1 vs. 2+) – Smoking history (Yes vs. No) – Histologic classification (adenocarcinoma vs. squamous cell carcinoma vs. large cell carcinoma) – Extent of disease (locally advance vs. metastatic) – Brain metastasis at baseline (Yes vs. No) – Number of prior treatments for advance disease	Crizotinib monotherapy (trial dose: 250 mg orally twice daily, continuously in 28-day cycles)	Platinum chemotherapy ± pemetrexed Pembrolizumab	Efficacy • ORR • **OS** • PFS • Duration of response • time to first tumour response • time to treatment failure Safety • AEs • SAEs • WDAE **Patient-reported outcomes/ QoL**
AE = adverse events; **ECOG** = Eastern Cooperative Oncology Group; **NSCLC** = non-small cell lung cancer; **ORR** = objective response rate; **OS**= overall survival; **QoL**=health-related quality of life; **PFS** = progression-free survival; **RCT**=randomized controlled trial; **SAE**=serious adverse events**; VEGF** = vascular endothelial growth factor**;** **WDAE**=withdrawal due to adverse events				

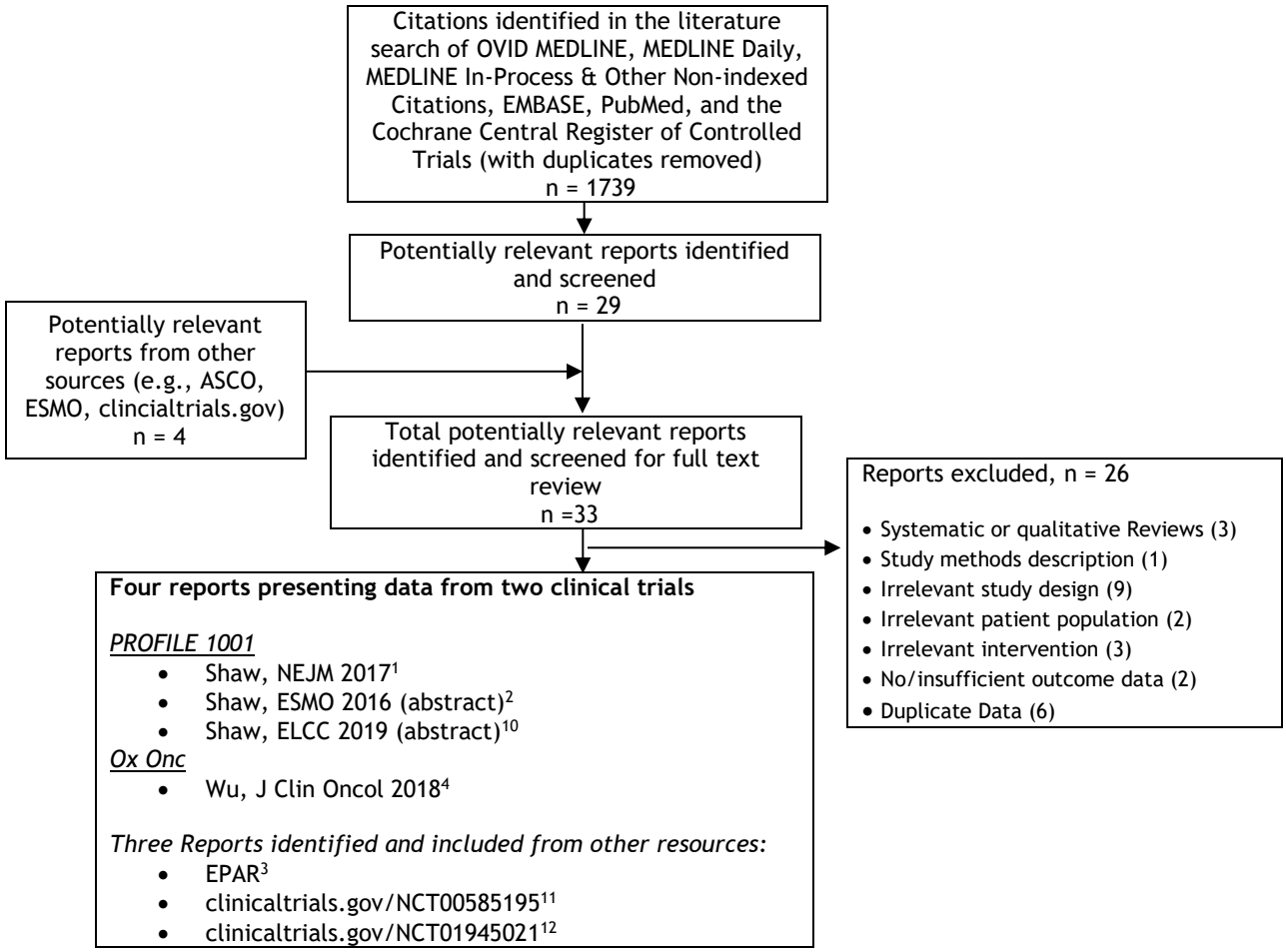
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 33 potentially relevant reports identified, seven reports were included in the pCODR systematic review.[1-4,10-12] and 26 reports were excluded. Studies were excluded because they were review articles or irrelevant study types,[5,13-23] described study methodology only,[24] included irrelevant population,[25,26] used irrelevant intervention,[27-29] or did not report data on outcomes and/or subgroups of interest.[30,31] Conference abstracts and journal articles reporting duplicate data from the included full articles were also excluded.[32-37] Figure 6.1 illustrates the PRISMA flow diagram for the study selection process.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the PROFILE 1001 and Ox Onc studies were also obtained through requests to the Submitter by pCODR[38,39]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: PROFILE 1001[1,2,10] NCT00585195[11] Characteristics: open label, multi-centre Phase I dose escalation, safety, pharmacokinetic and Pharmacodynamic Study N= 53 Number of centres and number of countries: eight centres across the United States, Australia and South Korea Patient Enrolment Dates: October 2010 to August 2013 Data cut-off: Efficacy: 16-May-2014 Safety: 11-April-2014 Updated analyses: 30- November-2014 30-June-2018 Final Analysis Date: NR Funding: Pfizer	Key Inclusion Criteria: • Age≥ 18 years • Histologically confirmed, advanced NSCLC with a ROS1 rearrangement • ECOG performance status 0 to 2 Key Exclusion Criteria: • Major surgery, radiation therapy or anti-cancer therapy within 2 to 4 weeks of starting study treatment, depending on the patient cohort • Prior stem cell transplant except of patients with neuroblastoma, lymphoma or myeloma • Active or unstable cardiac disease or heart attack within 3 months of starting study treatment	Intervention: Crizotinib 250 mg twice daily in continuous 28-day cycles. Comparator: None	Primary: • ORR (by investigator) • Safety Secondary: • PFS • OS
Study: Ox Onc[4] NCT01945021[12] Characteristics: phase II, open label, single-arm study N= 127 Number of centres and number of countries: 37 sites in China, Japan, South Korea, and Taiwan Patient Enrolment Dates: September 2013 to January 2015 Data cut-off: 30-July-2016 Final Analysis Date: NR Funding: Pfizer	Key Inclusion Criteria: • Age≥ 18 years • Histologically or cytologically confirmed, advanced NSCLC with a ROS1 rearrangement • Treatment-naïve or have received no more than 3 systemic treatment regimen(s) • ECOG performance status 0 to 1 Key Exclusion Criteria: • Prior therapy specifically directed against ALK or ROS1 fusion genes	Intervention: Crizotinib 250 mg twice daily in continuous 28-day cycles. Comparator: None	Primary: • ORR (by IRR) Secondary: • DOR • TTR • DCR • PFS • OS • QoL • Safety

DOR = duration of response; **DCR** = disease control rate (percentage of patients with a confirmed complete or confirmed partial response or stable disease; **ECOG** = Eastern Cooperative Oncology Group**; IRR =** independent radiologic review**; NR** = not reported; **NSCLC** = non-small cell lung cancer; **ORR** = objective response rate; **OS** =

overall survival; **PFS** = progression-free survival; **TTR** = time to first tumour response

Table 6.3: Select quality characteristics of included studies of [drug] in patients with [disease]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
PROFILE 1001[1,2,10]	crizotinib vs. no comparator	ORR	30	53	NA	NA	NA	Yes	No	No	Yes
Ox Onc[4]	crizotinib vs. no comparator	ORR	110	127	NA	NA	NA	No	Not available	NA	Yes

a) Trials

PROFILE 1001[1,2]

PROFILE 1001 is an open label, multi-centre Phase I dose escalation, safety, pharmacokinetic and pharmacodynamics study. The study was originally designed to include an initial dose-escalation phase, followed by an expansion phase with the maximum dose, which was established in the dose escalation phase, in molecularly defined cohorts of study participants (e.g., ALK-positive expansion cohort). In November 2009, the study was amended to include advanced NSCLC patients with tumors having an ROS1 gene translocation. ROS1 rearrangement was identified using break-apart fluorescence in situ hybridization (FISH) or a reverse-transcriptase–polymerase-chain reaction (RT-PCR) assay.

PROFILE 1001 was conducted in eight Centres across the United States, Australia and South Korea. Patients in ROS1 expansion cohort were enrolled from eight sites in three countries (Australia and South Korea one centre each, and six centres in the United States).[1,3]

A sample size of approximately 30 patients (of whom 27 evaluable) was originally planned to achieve at least 85% power to test the null hypothesis of ORR ≤0.10 vs. the alternative hypothesis of ORR> 0.10, with one-sided α=0.05. An alternative target rate of 0.30 was assumed using a single stage design. The null hypothesis was to be rejected if greater than or equal to six objective responses were observed among the initially 27 evaluable patients. The sample size was subsequently increased to a total of 50 patients (Amendment #20) in order to provide a more robust estimation of efficacy in this patient population.[3]

The primary endpoint of the PROFILE 1001 ROS1 expansion study was response rate, determined according to the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety. Patients underwent tumour assessment at baseline, and every 8 weeks until cycle 15, and every 16 weeks thereafter until RECIST-defined disease progression. Tumour assessments were performed using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis. Brain and bone scans were obtained at baseline if disease at these sites was suspected. All tumor responses were confirmed at least four weeks after the initial response.

The following response variables were measured and reported using the RECIST criteria:

- Complete Response (CR), defined as disappearance of all target and non-target lesions, normalization of tumor marker levels, and no appearance of new lesions (each must be documented on two occasions, at least four weeks apart).
- Partial Response (PR), defined as ≥30% decrease in the sum of the longest diameters of target lesions (compared to the baseline sum, as reference), without progression of non-target lesions and no appearance of new lesions (each must be documented on two occasions, at least four weeks apart.
- Stable Disease (SD), where neither PR nor PD criteria were met
- Progressive Disease (PD): defined as ≥20% increase in the sum of the longest diameter of target lesions (when compared to the smallest sum of longest diameters recorded since the treatment started, as reference), unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

Adverse events (AEs) were assessed at the time of informed consent until at least 28 days after the last dose of crizotinib and were evaluated using Common Terminology Criteria for Adverse Events, version 3.0. Additional molecular analyses were performed in patients with sufficient tumour tissue samples.

The sample size was originally calculated at 30 patients to provide a power of at least 85%, at a one-sided alpha level of 0.05 and with the use of a single-stage design, to reject the null hypothesis that the rate of response to crizotinib would be 10% or less, versus the alternative hypothesis that the response rate would be more than 10% (assuming a 30% response rate for the alternative hypothesis). Patient enrollment was started in October 2010. As of April 2012, there were eight responses (among 14 evaluable patients), which exceeded the six responses required to reject the null hypothesis. The investigators then expanded the sample size to a maximum of 50 patients to "permit a more accurate assessment of the efficacy and safety of crizotinib in this population".

Kaplan Meier analysis of time-to-event data was used to estimate median event times; and the Brookmeyer–Crowley method was used to calculate two-sided 95% confidence intervals.

The data cut-off dates for the efficacy and safety data were 16-May-2014 and 11-April- 2014, respectively. The results from these analyses were published in November 2014 by Shaw et al.[1] The results from PROFILE 1001 was updated on 30-November-2014[2,39] and 30-June-2018[10] data cut-off dates.

Ox Onc[4]

Ox Onc was a phase II, open label, single-arm study that enrolled East Asian patients with ROS1-positive advanced NSCLC who received ≤ 3 prior lines of systemic therapies. The trial was conducted in 37 sites in China, Japan, South Korea, and Taiwan.

The primary endpoint of the Ox Onc trial was objective response rate (ORR), defined as the number of patients with a best overall response of confirmed CR or confirmed PR according to RECIST v1.1 as determined by Independent Radiology Review (IRR). All tumor responses were confirmed at least four weeks after the initial response. Secondary endpoints included duration of response (DOR), time to first tumour response (TTR), disease control rate (DCR, percentage of patients with a confirmed complete or confirmed partial response or stable disease), progression-free survival (PFS), and overall survival (OS). Safety and patient-reported outcomes were also evaluated.

Tumor assessments were performed at baseline, every 8 weeks until cycle 8, and every 12 weeks thereafter until disease progression by IRR (RECIST defined) or treatment discontinuation. Brain

and bone scans were to be performed at screening. For patients with bone or brain lesions at baseline, repeat scans were to be taken every 8 weeks (brain scans) or 12 weeks (bone scans).AEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Patient-related outcomes (PROs) for disease and treatment-related symptoms, functioning, and global quality of life (QOL) were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and the corresponding Lung Cancer Module (QLQ-LC13).

A 30% ORR was considered as a clinically meaningful threshold for this study; i.e., the null hypothesis would be rejected if the lower limit of the two-sided 95% CI for the observed ORR was greater than this threshold (which would demonstrate the efficacy of crizotinib). The sample size was calculated by assuming a 50% true ORR. With 100 evaluable patients, the statistical power to demonstrate efficacy on the basis of this threshold was 98.2%. The projected enrollment was 110 patients.

The safety analysis was performed using data from all enrolled patients who received at least one dose of crizotinib. The response-evaluable population was defined as all patients in the safety analysis population who had an adequate baseline tumor assessment. ORR and DCR by IRR were evaluated in the response-evaluable population, and the 95% CIs were calculated using the exact method on the basis of the F-distribution. DOR and TTR were assessed only in the subgroup of responder-patients in the response-evaluable population. Descriptive statistics and Kaplan-Meier method were used to summarize DOR; and TTR was summarized using descriptive statistics only. The Kaplan-Meier method was used to estimate median PFS and OS in the safety analysis population.

PROs were analyzed in the PRO-evaluable population which included all patients in the safety analysis population who completed a baseline and one or more post–baseline PRO assessments. Changes in EORTC QLQ-C30 and QLQLC13 scores of ≥ 10 points from baseline were considered clinically meaningful. PROs were considered statistically significant if the 95% CIs for changes in EORTC scores from baseline did not include 0.

The study began in September 2013; the cut-off date for the analysis published by Wu et al[4] was 30-July-2016.

b) Populations

PROFILE 1001[1]

To be eligible for participation in the PROFILE 1001 ROS1 expansion cohort, patients had to have at least 18 years of age, a histologically confirmed advanced NSCLC with a ROS1 rearrangements, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2, measurable disease according to RECIST(version 1.0), and adequate organ function.

A total of 53 patients with ROS1-positive NSCLC were enrolled from 15-October-2010 to August 2013. Three additional patients were enrolled in another expansion cohort of the PROFILE 1001 study (ALK negative cohort #2) and were retrospectively identified to be ROS1-positive and, thus, were included in the analysis of ROS1-positive NSCLC patients.[3,39]

Baseline characteristics of the 53 study population are summarized in Table 6.4. The median age for the ROS1 expansion cohort was 55 years (range 25 to 81). The majority of patients were White (56.6%) or Asian (39.6%), and never smokers (75.5%). All patients presented with measurable disease; 96.2% had adenocarcinoma histology; and 86.8% had received at least one prior line of treatment.

A summary of the types and frequencies of prior anticancer therapies is provided in Table 6.5.

Table 6.4: Baseline characteristics of patients in the PROFILAE 1001 trial

	ROS1-positive NSCLC, 250 mg BID (N=53)
Sex, n (%)	
Male	23 (43.4)
Female	30 (56.6)
Age (years)	
n	53
Mean (SD)	54.1 (13.44)
Median	55.0
Range	25-81
Age Category (years), n (%)	
<65	38 (71.7)
≥65	15 (28.3)
Race, n (%)	
White	30 (56.6)
Black	2 (3.8)
Asian	21 (39.6)
Racial designation for Asian	
Korean	13 (24.5)
Chinese	4 (7.5)
Other	4 (7.5)
Weight (kg)	
n	53
Mean (SD)	71.9 (15.97)
Median	70.0
Range	48.0-106.3
Smoking Classification, n (%)	
Never smoked	40 (75.5)
Ex-smoker	13 (24.5)
ECOG Performance Status, n (%)[a]	
0	23 (43.4)
1	29 (54.7)
2	1 (1.9)

Source: Section 14.1, Tables 14.1.2.1.1.1.ros, 14.1.2.1.2.1.ros, and 14.1.2.4.1.ros.
Weight is based on the information collected at screening from the Demographics CRF page.
Abbreviations: BID=twice daily; CRF=case report form; ECOG=Eastern Cooperative Oncology Group; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer; SD=standard deviation.
a Baseline is the Cycle 1 Day 1 value, unless missing, then Baseline is the Screening value.

Source:[EMA assessment report, Table 7. Page 23/70][3]

Table 6.5: Summary of previous anticancer therapies in the PROFILE 1001 trial

	ROS1-positive NSCLC, 250 mg BID N=53 n (%)
Prior surgeries	
Yes	53 (100)
Prior radiation therapies	
No	34 (64.2)
Yes	19 (35.8)
Prior systemic advanced/metastatic therapies	
No	7 (13.2)
Yes	46 (86.8)
Number of regimens	
1	20 (37.7)
2	13 (24.5)
3	3 (5.7)
4	2 (3.8)
5	5 (9.4)
6	3 (5.7)

Source: Section 14.4, Table 14.4.2.2.1.ros.
Patients could have reported more than 1 type of prior treatment.
Abbreviations: BID=twice daily; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.

Source:[EMA assessment report, Table 8. Page 24/70][3]

Ox Onc[4]

To be eligible for the ONC study, patients had to have at least 18 years of age, a histologically or cytologically confirmed locally advanced or metastatic NSCLC with a ROS1 rearrangements and negative for ALK rearrangements, an ECOG performance score of 0 or 1, ≤3 prior systemic therapies for advanced-stage disease, one or more measurable tumor lesions according to RECIST (version 1.1), and no previous radiation therapy. Patients with brain metastases were eligible if asymptomatic or were neurologically stable for ≥2 weeks (if treated). Prior therapies with an activity against ALK or ROS1 mutations were not permitted.

Between September 2013 and January 2015, 127 patients with ROS1-positive NSCLC were enrolled and received one or more doses of crizotinib. Baseline characteristics of the study population are summarized in Table 6.6. All patients included in this study were Asian (58.3% from China, 20.5% from Japan, and the remaining 21.3% from South Korea and Taiwan). The median age was 51.5 years (range 23 to 80); the majority of patients were never smokers (71.7%), had adenocarcinoma histology (97.6%), had metastatic disease (95.3%), and had received at least one prior line of treatment (81.1%)

Table 6.6: Baseline characteristics of patients in the Ox Onc trial

Table 1. Baseline Patient Characteristics and Demographics

Characteristic	Total, No. (%)	Japan, No. (%)	China, No. (%)	Other,* No. (%)
No. of patients	127	26	74	27
Age, years				
Median	51.5	56.3	49.5	52.7
Range	22.8-79.7	30.2-79.1	22.8-79.7	33.8-73.8
Age group				
< 65 years	106 (83.5)	17 (65.4)	65 (87.8)	24 (88.9)
≥ 65 years	21 (16.5)	9 (34.6)	9 (12.2)	3 (11.1)
Sex				
Male	54 (42.5)	10 (38.5)	34 (45.9)	10 (37.0)
Female	73 (57.5)	16 (61.5)	40 (54.1)	17 (63.0)
Smoking history				
No	91 (71.7)	16 (61.5)	55 (74.3)	20 (74.1)
Yes	36 (28.3)	10 (38.5)	19 (25.7)	7 (25.9)
ECOG PS at baseline				
0	34 (26.8)	10 (38.5)	9 (12.2)	15 (55.6)
1	93 (73.2)	16 (61.5)	65 (87.8)	12 (44.4)
Histologic classification				
Adenocarcinoma	124 (97.6)	26 (100.0)	71 (95.9)	27 (100.0)
Squamous cell carcinoma	1 (0.8)	0 (0.0)	1 (1.4)	0 (0.0)
Large-cell carcinoma	2 (1.6)	0 (0.0)	2 (2.7)	0 (0.0)
Extent of disease				
Locally advanced only	6 (4.7)	0 (0.0)	4 (5.4)	2 (7.4)
Metastatic	121 (95.3)	26 (100.0)	70 (94.6)	25 (92.6)
Brain metastases at baseline†				
Yes	23 (18.1)	3 (11.5)	12 (16.2)	8 (29.6)
No. of prior regimens for advanced disease				
0	24 (18.9)	2 (7.7)	18 (24.3)	4 (14.8)
1	53 (41.7)	14 (53.8)	27 (36.5)	12 (44.5)
2	31 (24.4)	6 (23.1)	17 (21.6)	8 (29.6)
3	19 (15.0)	4 (15.4)	12 (17.6)	3 (11.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*Includes patients enrolled in South Korea and Taiwan.
†By independent radiology review.

Wu, Y.L. et al: J Clin Oncol. 36(14):1405-1411.

c) Interventions

PROFILE 1001[1]

For patients in the expansion cohort of the PROFILE 1001 trial, crizotinib was administered orally at the standard dose of 250 mg twice daily in continuous 28-day cycles. Treatment continued until RECIST-defined disease progression or clinical deterioration, unacceptable toxic effects, withdrawal from the study, or death. Patients with disease progression could continue to receive crizotinib at the investigator's discretion and with approval from the sponsor.

As of 30-November-2014 data cut-off date, the median duration of treatment was 64.5 weeks (range 2.3 to 182.0), and 30 out of 50 patients (60%) continued to receive crizotinib after the data cut-off date.

According to the study protocol, patients with disease progression could continue to receive crizotinib at the investigator's discretion. pCODR requested information on the number and proportion of patients who were treated with crizotinib beyond disease progression; however, the submitter stated that this data was not available for the PROFILE 1001 trial ROS1 positive expansion cohort.[39] The submitter was also unable to provide a summary of other post-discontinuation disease-related anticancer therapies for patients in this cohort.[39]

Ox Onc[4]

Crizotinib was administered at a dose of 250 mg twice daily in continuous 28-day cycles. Treatment continued until RECIST-defined disease progression (determined by IRR), unacceptable toxicity, or withdrawal of consent. Patients with disease progression could continue to receive crizotinib at the investigator's discretion, if they had ongoing clinical benefit.

As of 30-July-2016 data cut-off date, the median duration of treatment was 19.7 months (95%CI, 14.1, not reached). 43 of the 63 patients (68.3%) who continued crizotinib post progression remained on treatment for a median of 20.7 weeks (range 3.3 to 92.7 weeks)

pCODR requested information on the number and proportion of patients who received post-discontinuation disease-related anticancer therapies; however, the submitter stated that they did not have access to this information and therefore, were unable to provide this data.[39]

d) Patient Disposition

PROFILE 1001

A total of 53 patients with advanced NSCLC were enrolled in the ROS1 expansion cohort.[3] As of 30-November-2014 data cut-off date, 47.2% of patients were alive and in follow-up; 52.8% were discontinued the study treatment mainly due to disease progression (24.5%). Other reasons for discontinuation are summarized in Table 6.7.[3]

Table 6.7: Patient disposition in the PROFILE 1001 ROS1 expansion cohort (Safety Population)

	ROS1-positive NSCLC, 250 mg BID N=53 n (%)
Ongoing in the study at data cutoff	25 (47.2)
Discontinued	28 (52.8)
Reason for discontinuation	
Adverse event	1 (1.9)
Lost to follow-up	1 (1.9)
Progressive disease	13 (24.5)
Patient died	2 (3.8)
Patient no longer willing to participate in the study	5 (9.4)
Other[a]	6 (11.3)

Source: Section 14.1, Table 14.1.1.3.1.ros.
Abbreviations: BID=twice daily; n=number of patients with data; N=total number of patients in population; NSCLC=non-small cell lung cancer.
a Other is 3 patients with clinical progression and 3 patients who switched to a commercial supply of crizotinib.

Source: [EMA assessment report, Table 5. Page 21/70][3]

Ox Onc[4]

A total of 127 patients with ROS1-positive NSCLC were enrolled in the trial. As of the 30-July 2016 data cu-off date, 59.8% of patients were alive and in follow-up for OS. pCODR requested detailed information on patient disposition for the Ox ONC trial; however, the submitter stated that they did not have access to this information and, therefore, were unable to provide this data.[39]

e) Limitations/Sources of Bias

The PROFILE 1001 and Ox Onc trials were relatively well-designed trials with clearly-defined study questions, eligibility criteria and study outcomes. However, the following study limitations should be taken into account when interpreting the results:

- PROFILE 1001 and Ox Onc were open-label phase I and phase II trials, respectively. The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments. This could particularly be important in reporting of subjective outcomes by the patients (e.g., patient-reported outcomes in OxOnc) and care providers (e.g., selective reporting of treatment-related AEs in both trials). In addition, PROFILE 1001 is a phase I dose escalation/expansion trial. Phase I trials are designed to detail toxicities and identify a tolerable range of potentially effective doses efficacy testing in phase II trials.
- Both PROFILE 1001 and Ox Onc were single arm studies with no active treatment or placebo control groups. As a result, a direct comparison of the efficacy and safety of crizotinib relative to the comparators identified in the review protocol (i.e., platinum - pemetrexed chemotherapy, and pembrolizumab) is not possible. Of note, no indirect treatment comparisons comparing crizotinib to potentially relevant comparators were provided by the submitter.
- In both trials, the assessments of tumor response and disease progression (ORR and PFS) were conducted by the investigators. However, to reduce the chance of performance bias,

both trials attempted to mitigate performance bias by using an independent radiology review board to assess response outcomes using standardized RECIST criteria.

- The Ox Onc trial collected PRO data, using validated and reliable tools. However, this data should be considered exploratory as the trial was not powered to detect statistically significant differences from the baseline in PROs.
- Both trials are the general subject to bias when it comes to the analysis of data from patients who did not receive a prior systemic therapy, due to the small number of treatment-naïve patients in the included trials, with no subgroup analysis results available from the Ox Onc trial for treatment-naïve patients. The majority of study participants had received≥ 1 prior regimen.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy outcomes for each of the included studies are presented blow.

PROFILE 1001[1,2]

Response Outcomes

At the 16-May-2014 data cut-off date, ORR based on investigator assessment was 72% (95% CI 58%, 84%); including three patients (6%) with a CR, 33 patients (66%) with a PR, and nine patients (18%) with SD. The median TTR was 7.9 weeks (range 4.3 to 32.0); and the estimated median DOR was 17.6 months (95% CI 14.5, not reached). At the time of data cut-off, 23 of the 36 responses (64%) were ongoing.[1]

The updated results PROFILE 1001 that presented at the ESMO 2016 Congress were based on a cohort of 53 study participants. At the 30-November-2014 data cut-off date, the ORR in this cohort was 69.8% (95% CI 55.7, 81.7), including five patients with CR, 32 patients with PR and 11 patients with SD (Table 6.8). The median TTR was 7.9 weeks (range 4.3 to 32.0); and the estimated median DOR was 17.6 months (range; 2.8 to 18.1)[2,3]

Subgroup analyses of ORR based on various baseline patient characteristics are shown in Table 6.9.

Table 6.8: Summary of confirmed responses in the PROFILE 1001 trial

Efficacy Parameter	Crizotinib (N=53)
Best Response, n (%)	
Complete response	5 (9.4)
Partial response[a]	32 (60.4)
Stable disease[b]	11 (20.8)
Objective progression[c]	3 (5.7)
Early death	1 (1.9)
Indeterminate	1 (1.9)
ORR (CR + PR), n (%) [95% CI][d]	37 (69.8) [55.7, 81.7]
DCR (CR+PR+SD) at Week 8, n (%) [95% CI][d]	46 (86.8) [74.7, 94.5]
DCR (CR+PR+SD) at Week 16, n (%) [95% CI][d]	42 (79.2) [65.9, 89.2]

Source: Study 1001 ROS1 CSR Tables 14, 14.2.1.1.ros and 14.2.2.ros.

Source: [EMA assessment report, Table 12. Page 28/70][3]

Table 6.9: Subgroup analysis of ORR in the PROFILE 1001 trial

	ROS1-positive NSCLC, 250 mg BID (N=53)	
	n/N*	ORR % (95% exact CI)[a]
Number of prior advanced/metastatic therapies		
0	6/7	85.7 (42.1, 99.6)
≥1	31/46	67.4 (52.0, 80.5)
ECOG PS at baseline		
0	18/23	78.3 (56.3, 92.5)
1	19/29	65.5 (45.7, 82.1)
2	0/1	0 (0.0, 97.5)
Age group		
<65 years	27/38	71.1 (54.1, 84.6)
≥65 years	10/15	66.7 (38.4, 88.2)
Gender		
Male	17/23	73.9 (51.6, 89.8)
Female	20/30	66.7 (47.2, 82.7)
Race group		
Asian	15/21	71.4 (47.8, 88.7)
Non-Asian	22/32	68.8 (50.0, 83.9)

Source: Section 14.2, Tables 14.2.1.2.ros, 14.2.1.3.ros, 14.2.1.4.ros, 14.2.1.5.ros, and 14.2.1.6.ros.
Best overall response is based on the investigator tumor assessment.
Abbreviations: BID=twice daily; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; n=number of patients with data; N=total number of patients in population; N*=number of patients in subgroup; NSCLC=non-small cell lung cancer; ORR=objective response rate; PS=performance status.
a Using exact method based on F-distribution.

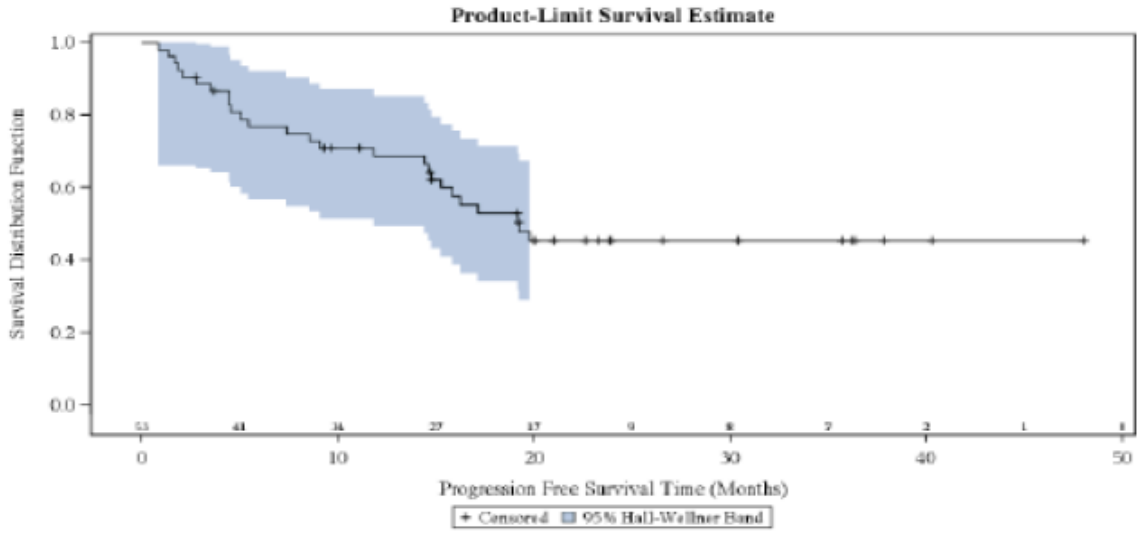
Source: EMA assessment report, Table 24. Page 35/70[3]

Progression-Free Survival (PFS)

As of the 16-May-2014 data cut-off date, the median PFS was 19.2 months (95% CI 14.4, not reached), and 25 patients (50%) were still in follow-up for disease progression. The Kaplan-Meier curve for PFS is shown in Figure 6.2.[1]

As of the 30-November-2014 data cut-off date (updated analysis; N=53), after median follow-up of 25.4 months, 26 (49.1%) of patients had a PFS event (23 patients with objective disease progression and 3 death). A total of 21 patients (39.6%) were still in PFS follow up at the time of the data cu-off. The median PFS was 19.3 months (95% CI 14.8,-not reached).[2,3]

Figure 6.2: Progression-free survival in the PROFILE 1001 trial



Source: Section 14.2, Figure 14.2.2.1.ros.
Note: tumor assessment is based on the derived tumor assessment using RECIST version 1.0 criteria and (for the 3 patients included from the ALK-negative NSCLC cohort only) RECIST version 1.1 criteria.
Numbers above the x-axis are numbers of patients at risk.
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; RECIST=Response Evaluation Criteria in Solid Tumors.

Source: EMA assessment report, Figure 4. Page 33/70[3]

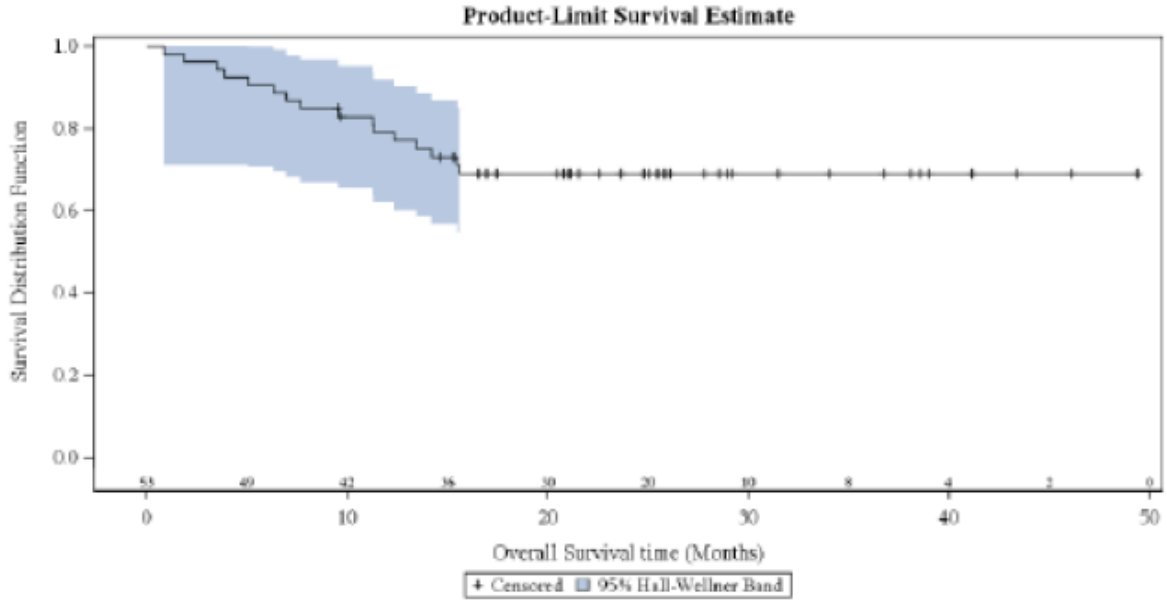
Overall Survival (OS)

At the 16-May-2014 data cut-off date, after a median follow-up of 16.4 months (95% CI 13.8, 19.8), 9/50 patients (18%) had died. The overall survival rate at 12 months was reported to be 85% (95% CI 72%, 93%); the median OS was not reached.[1]

As of the 30-November-2014 data cut-off date (updated analysis; N=53), after a median follow-up of 25.4 months (95% CI 22.5, 28.5), 16 (30.2%) patients had died. The 6-month and 12-month OS rates were 91% (95% CI 79%, 96%) and 79% (95% CI 65%, 88%), respectively.[2,3] The Kaplan-Meier curve for OS is shown in Figure 6.3.

As of the 30-June-2018 data cut-off date, after a median follow-up period of 63 months, a total of 26 patients (49.1%) had died. The median OS was 51 months (95% CI 29, not estimable), with the OS probabilities at 12, 24 and 48 months being 78.8%, 67.0% and 50.7%, respectively.[10]

Figure 6.3: Overall survival in the PROFILE 1001 trial



Source: Section 14.2, Figure 14.2.3.1.ros.
Numbers above the x-axis are numbers of patients at risk.
Abbreviations: NSCLC=non-small cell lung cancer.

Source: EMA assessment report, Figure 5. Page 34/70[3]

Subgroup analyses of OS, based the number of prior regimens for advance disease (treatment-naïve versus ≥1 line of prior therapies), are presented in Table 6.10.

Table 6.10: Overall survival by the number of prior advanced/metastatic therapies

	ROS1-Positive, NSCLC, 250 MG BID (N=53)	
	Untreated	**Pretreated ≥1 line**
Number (%) of Subjects	7 (13.2)	46 (86.8)
Number of Deaths	2 (28.6)	14 (30.4)
Number censored	5 (71.4)	32 (69.6)
• Subject remain in follow up	4 (57.1)	29 (63.0)
• Subject no longer willing to participate	1 (14.3)	0
• Lost to follow-up	0	1 (2.2)
• Completed required 1 year follow up	0	2 (4.3)

Source: EMA assessment report, Table 23. Page 35/70[3]

Ox Onc[4]

Response Outcomes

At the 30-July-2016 data cut-off date, ORR based on IRR was 71.7% (95% CI 63.0%, 79.3%), including 17 patients (13.4%) with a CR, 74 patients (58.3%) with a PR, and 21 patients (16.5%) with SD. ORR met the pre-defined clinically meaningful threshold for this study (i.e., the lower bound of the two-sided 95% CI for ORR acceded the pre-defined clinically meaningful threshold of 30%). Subgroup analysis by demographic and disease characteristics showed that the ORR benefit

was observed irrespective of the presence of brain metastases at baseline, number of prior lines of chemotherapy, country of enrollment, age, sex, smoking status, or ECOG performance status (Table 6.11).

The median TTR was 1.9 months (range 1.6 to 15.8), and the median DOR was 19.7 months (95% CI 14.1, not reached).

Table 6.11: Subgroup analyses of ORR in the Ox Onc trial

Table 3. Independent Radiology Review–Assessed ORR by Baseline Characteristics

Characteristic	Total Crizotinib (N = 127)	
	No. of Patients	ORR, % (95% CI)
Country		
China	53 of 74	71.6 (59.9 to 81.5)
Japan	17 of 26	65.4 (44.3 to 82.8)
Other	21 of 27	77.8 (57.7 to 91.4)
Sex		
Male	34 of 54	63.0 (48.7 to 75.7)
Female	57 of 73	78.1 (66.9 to 86.9)
Age-group		
< 65 years	78 of 106	73.6 (64.1 to 81.7)
≥ 65 years	13 of 21	61.9 (38.4 to 81.9)
Smoking history		
No	68 of 91	74.7 (64.5 to 83.3)
Yes	23 of 36	63.9 (46.2 to 79.2)
Baseline ECOG PS		
0	24 of 34	70.6 (52.5 to 84.9)
1	67 of 93	72.0 (61.8 to 80.9)
Brain metastases at baseline		
Yes	17 of 23	73.9 (51.6 to 89.8)
No	74 of 104	71.2 (61.4 to 79.6)
No. of prior regimens for advanced disease		
< 2	56 of 77	72.7 (61.4 to 82.3)
≥ 2	35 of 50	70.0 (55.4 to 82.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PS, performance status.

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Disease Control Rate (DCR)

Disease control rate was 88.2 (95% CI 81.3, 93.2) at Week 8 and 80.3 (95% CI 72.3, 86.8) at Week 16 after initiation of crizotinib.

Progression-Free Survival (PFS)

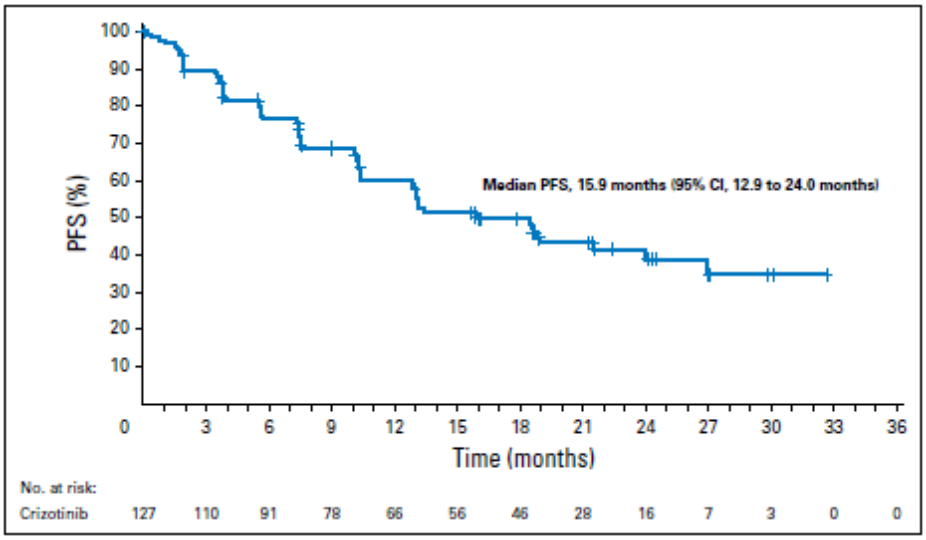
As of the 30-July-2016 data cut-off date, the median PFS was 15.9 months (95%CI 12.9, 24.0), and 45 patients (35.4%) were still in follow-up for disease progression. The Kaplan-Meier curve for PFS is shown in Figure 6.4.

Overall Survival (OS)

At the 30-July-2016 data cut-off date, after a median follow-up of 21.4 months (95% CI 20.1 to 23.0) for OS, 39 patients (30.7%) had died during the study. The median OS was 32.5 months (95%

CI 32.5, not reached). The 6-month and 12-month OS rates were 92.0% (95% CI 85.7%, 95.6%) and 83.1% (95% CI 75.2%, 88.6%), respectively.

Figure 6.4: Progression-free survival in the PROFILE 1001 trial



Wu, Y.L. et al: J Clin Oncol. 36(14):1405-1411.

Quality of Life/patient reported outcomes (PROs)

PROs were not measured in the PROFILE 1001 trial.

Ox Onc[4]

PRO results were reported for the first 20 cycles due to the scarcity smaller numbers of patients in the later cycles of treatment. During the first 20 treatment cycles, 99% to 100% of patients completed at least one question from the EORTC QLQ-C30 and QLQ-LC13.

PRO-evaluable population included 123 patients. Figure 6.5 illustrates changes from the baseline in global QoL. Improvements in global QOL were statistically significant at cycles 3 to 5, 7, and 10. Clinically meaningful improvements (defined as ≥ 10 points change) were observed in patient-reported EORTC QLQC30 scores for insomnia, dyspnea symptoms at several time points over the first 20 cycles. Clinically meaningful improvements were observed in EORTC QLQ-LC13 scores for patient-reported symptoms of cough (cycles 2 to 8, 10, 12, 14, 16, 18, and 20) and pain in chest (cycles 16, 18, and 20).

Other statistically significant PROs improvements included fatigue (cycles 3 to 8, 10, 12, 14, 16, 18, and 20), (cycles 2 to 8, 10, 12, 14, 16, 18, and 20), and appetite loss (cycles 4 to 6, 8, 12, 14, 16, and 18). A statistically significant and clinically meaningful deterioration from baseline was reported for constipations (cycles 2 to 4, 12, 16, and 18) and diarrhea (cycles 2 to 8, 10, and 16)..

Figure 6.5: Change from the baseline in global quality of life (PRO-evaluable population in the OXOnc trial)

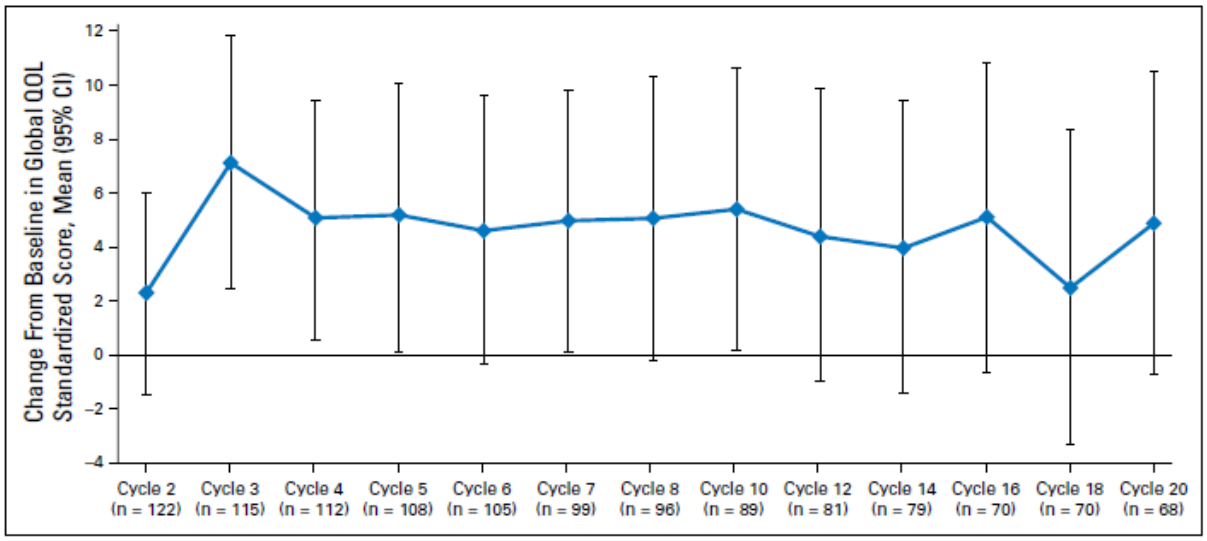


Fig A1. Change from baseline in global quality of life (QOL) standardized scores on the basis of the patient-reported outcomes–evaluable population at baseline (cycle 1). The number of patients who completed the scale at baseline and at respective cycles are shown.

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Harms Outcomes

PROFILE 1001[1,2,10]

The primary safety results presented in this section are based on the analysis of data from 50 staudy participants (11-April 2014), published by Shaw et al in the New England o Journal of Medicine in 2014.[1] The updated safety analysis included all 53 study participants.[10]

As of 11-April-2014 data cut-off date, the median duration of treatment was 64.5 weeks (range 2.3 to 182.0), and 30 out of 50 patients (60%) remained on crizotinib after the data cut-off date.

Treatment- related AEs (as determined by the investigators) that were seen in at least 10% of the patients are summarized in Table 6.12. As shown in the table, the most common AEs were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), an elevated aspartate aminotransferase level (22%), fatigue (20%), dysgeusia (18%), and dizziness (16%). Overall, 365 out of the 388 treatment-related adverse events (94%) were grade 1 or 2.

The most frequently reported treatment-related grade 3 AEs (reported in ≥4% of patients) included hypophosphatemia (10%), neutropenia (10%), and an elevated alanine aminotransferase level (4%). No grade 4 or 5 treatment-related AEs were reported. Non-treatment related grade 4 AEs that were reported in four patients included pulmonary embolism, hypoxemia, hypotension, and pericardial effusion. One patient (2%) discontinued crizotinib due to treatment-related nausea. Five patients died, all due to disease progression. The deaths were considered to be unrelated to the treatment. No serious adverse events or deaths were observed in the 5-week period between the cut-off date for safety data and the cut-off date for efficacy data.

Table 6.12: summary of adverse events reported in the PROFILE 1001 trial

Table 2. Adverse Events.*

Adverse Event	Grade 1	Grade 2	Grade 3	All Grades
	number of patients (percent)			
Visual impairment	41 (82)	0	0	41 (82)
Diarrhea	21 (42)	1 (2)	0	22 (44)
Nausea	18 (36)	2 (4)	0	20 (40)
Peripheral edema	15 (30)	5 (10)	0	20 (40)
Constipation	16 (32)	1 (2)	0	17 (34)
Vomiting	15 (30)	1 (2)	1 (2)	17 (34)
Elevated aspartate aminotransferase	9 (18)	1 (2)	1 (2)	11 (22)
Fatigue	9 (18)	1 (2)	0	10 (20)
Dysgeusia	9 (18)	0	0	9 (18)
Dizziness	8 (16)	0	0	8 (16)
Elevated alanine aminotransferase	3 (6)	2 (4)	2 (4)	7 (14)
Hypophosphatemia	0	2 (4)	5 (10)	7 (14)
Decreased testosterone†	2 (9)	1 (5)	0	3 (14)
Neutropenia	1 (2)	0	5 (10)	6 (12)
Dyspepsia	5 (10)	0	0	5 (10)
Sinus bradycardia	5 (10)	0	0	5 (10)

* Listed are adverse events that were reported in at least 10% of the 50 study patients and that were deemed by the investigators to be related to treatment. No grade 4 or grade 5 treatment-related adverse events were reported.
† The frequency of a decreased testosterone level was calculated in 22 men only. The protocol did not require the testing of testosterone, so not all men were evaluated.

From: N Engl J Med, Shaw A.T. et al., Crizotinib in ROS1-rearranged non-small-cell lung cancer, 371(21):1963-1971. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

At of the 30-June-2018 data cut-off date, after a 22 months (95% CI 15, 36) median duration of treatment, no new safety signals were noted. The most common grade 3 treatment-related AEs (reported in ≥5% of patients) included hypophosphatemia (15.1%) and neutropenia (9.4%). No grade 4 treatment-related AEs were reported. During the longer-term follow up no new death events or withdrawals due to AEs were reported.[10]

Ox Onc

At the data cut-off date, the median duration of crizotinib treatment was 18.4 months (range 0.1 to 34.1). Treatment- related AEs (as determined by the investigators) that were seen in at least 10% of the patients are summarized in Table 6.13.

As shown, treatment-related AEs occurred in 96.1% of patients. The most frequently reported treatment-related AEs of any grade included elevated transaminases (55.1%), vision disorder (48.0%), nausea (40.9%), diarrhea (38.6%), and vomiting (32.3%). No cases of treatment-related pneumonitis were reported.

Grade 3 or 4 crizotinib-related AEs were reported in 32 patients (25.2%). The most common grade 3 or 4 treatment-related AEs were neutropenia (10.2%) and elevated transaminases (5.5%).

One patient (0.8%) permanently discontinued crizotinib due to diarrhea (grade 1 AE). Treatment-related AEs resulted in dose reductions and dose interruptions in 15.7% and 22.8% of patients, respectively.

By the time of the safety analysis, 39 patients (30.7%) had died during the study. Disease progression was the most common cause of death that occurred in 35 patients (27.6%). Other causes of death included: pneumonia in two patients (1.6%), respiratory failure in one patient (0.8%), and unknown in one patient (0.8%). No crizotinib-related deaths were reported in the Ox Onc trial.

Table 6.13: summary of adverse events reported in the Ox Onc trial

Table 4. Treatment-Related Adverse Events in Patients Treated With Crizotinib (n = 127)

Adverse Event	All Grades, No. (%)	Grade 3, No. (%)*	Grade 4, No. (%)
Any	122 (96.1)	28 (22.0)	4 (3.1)
In ≥ 10% of patients			
Elevated transaminases†	70 (55.1)	5 (3.9)	2 (1.6)
Vision disorder†	61 (48.0)	0 (0.0)	0 (0.0)
Nausea	52 (40.9)	2 (1.6)	0 (0.0)
Diarrhea	49 (38.6)	1 (0.8)	0 (0.0)
Vomiting	41 (32.3)	0 (0.0)	0 (0.0)
Constipation	38 (29.9)	0 (0.0)	0 (0.0)
Neutropenia†	37 (29.1)	11 (8.7)	2 (1.6)
Leukopenia†	29 (22.8)	3 (2.4)	0 (0.0)
Edema†	29 (22.8)	0 (0.0)	0 (0.0)
Dysgeusia	22 (17.3)	0 (0.0)	0 (0.0)
Decreased appetite	20 (15.7)	1 (0.8)	0 (0.0)
Blood creatinine increased†	19 (15.0)	0 (0.0)	0 (0.0)
Fatigue	15 (11.8)	1 (0.8)	0 (0.0)
Bradycardia†	13 (10.2)	2 (1.6)	0 (0.0)

*Other grade 3 treatment-related adverse events in ≥ 1% of patients were ECG QT prolonged (1.6%) and renal cyst† (1.6%).
†This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes, which are listed in Appendix Table A2 (online only).

Wu, Y.L. et al: J Clin Oncol. 36(14):1405-1411.

6.4 Ongoing Trials

No additional ongoing trials were identified relating to the use of crizotinib for first-line treatment of patients with ROS1-positive advanced NSCLC. The submitter provided the following list of ongoing studies investigating the benefit of crizotinib in previously-treated patients with ROS1-positive NSCLC

Table 6.14. Ongoing clinical trials of crizotinib in patients with ROS1-rearranged NSCLC

Clinical Trial	Design	Patient population	Sample size	Trial outcomes
AcSé NCT02034981[40]	Phase II, multi-tumour 2-stage design	Previously treated (progressed after at least 1 line standard treatment, including platinum-based doublet, unless patient considered unfit for chemo)	37	Primary: ORR Key Secondary outcomes: PFS OS Response duration
EUCROSS NCT02183870[41]	Phase II prospective trial	Previously treated (irrespective of the number of prior treatment lines)	29 (34 enrolled)	Primary: ORR Key Secondary outcomes Adverse events
METROS NCT02499614[42]	Phase II prospective trial	Failed at least 1 standard chemotherapy regimen	26	Primary: ORR Key Secondary outcomes: PFS OS

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified.

8 COMPARISON WITH OTHER LITERATURE

This section describes how the evidence and results summarized in the pCODR systematic review compare with published literature or other findings.

One report presenting data from an observational study was provided by the submitter. In the absence of comparative efficacy evidence, data from this study was used to inform the economic model. The Clinical Guidance panel also identified this study as being relevant, even though it did not meet the criteria for the systematic review.

Summary of the study:

EUROS1[5]

a) Study design

EUROS1 was a retrospective study conducted in six European countries (i.e., France, Switzerland, Italy, Germany, Poland, and the Netherlands). The study included a consecutive series of patients who were identified to have a *ROS1* rearrangement and treated with crizotinib (through an individual off-label use) in European centres that test for *ROS1*. Clinical and biologic data were retrospectively collected and analyzed in Toulouse, France, after being anonymized at the local centres. Histology was assessed locally by a specialist lung cancer pathologist and all reports were reviewed centrally.

For all patients, data were collected on patient and disease characteristics (i.e., age at diagnosis, date of diagnosis, tobacco consumption, and tumor stage), lines of systemic therapies, type of chemotherapy or targeted therapy, the date of initiation and end of treatment. Outcome variables of interest included recurrence and survival events. Data were also collected on best response (from the start of treatment until disease progression, according to RECIST version 1.1), and the occurrence of grade 4 or 5 toxicities. Patients needed to have undergone adequate follow-up visits that included thoracic and abdominal computed tomography scans at baseline and after 6 to 8 weeks of crizotinib therapy.

For categorical variables, data were summarized according to frequency and percentage; medians and ranges were used for continuous variables. Survival rates were estimated using the Kaplan-Meier method. PFS was measured as the time from the beginning of treatment to progression or death. Patients who were alive without progression at the time of analysis were censored at their last follow-up assessment.

b) Study Population

EUROS1[5]

Patients with ROS1 FISH-positive lung cancer treated with crizotinib through individual off-label use were identified and included in the EUROS1 study. All patients had stage IV disease at the time of crizotinib treatment, and were previously tested for EGFR, ALK, and KRAS mutations, and most were tested for BRAF, PI3KCA, HER2, and RET.

A total of 32 patients were included in the study. One patient, who was positive for KRAS and negative for breakpoint detection in ROS1 exons 31 to 34, was excluded from the analysis. The baseline patient and disease characteristics are shown in Table 8.1. The median age at diagnosis was of 50.5 years (range 34 to 78). Most patients were female (64.5%), never-smoker (71.0%), and had been diagnosed with a stage IV tumour (80.7%). All tumors were adenocarcinomas, including five tumours with a lepidic component and one tumor with composite adenosquamous histology. All patients but one had received at least one prior line of treatment (97%).

Table8.1: Baseline characteristics of patients in the EUROS1 study

Table 1. Clinical and Biologic Characteristics of Patients With Lung Cancer and a *ROS1* Rearrangement

Characteristics	No. of Patients (N = 31)	%
Age at diagnosis, years		
Mean	53.4	
Standard deviation	11.9	
Median	50.5	
Sex		
F	20	64.5
M	11	35.5
Tobacco use		
Never	22	71
Former	6	19.3
Current	3	9.7
Unknown	0	
Tumor stage (at the time of initial diagnosis)		
I	1	3.2
II	1	3.2
III	4	12.9
IV	25	80.7
Metastasis sites for stage IV disease	31	
Lung	5	16.2
Brain	1	3.2
Bone	2	6.5
Multiple organs	8	25.8
Lymph node	5	16.2
Pleural	3	9.7
Other or unknown	7	22.6
ROS1 detection methods		
IHC and FISH (France)	12	38.7
FISH alone	15	48.4
FISH and NGS	4	12.9

Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing.

Mazières, J. et al. J Clin Oncol. 33(9):992-999.

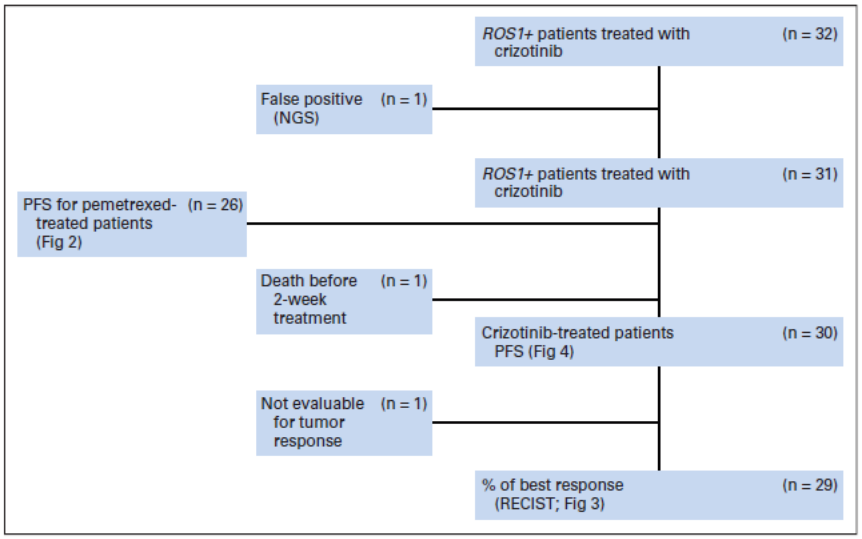
c) Intervention

All patients received crizotinib 250mg, twice daily, for a minimum duration of two weeks. Crizotinib was administered as a first- or second-line treatment in 10 patients (32%), and as third or further lines of therapy in 21 patients (68%). All patients had progressive disease at the time of crizotinib initiation, except one patient who was chemotherapy-naive.

d) Patient Disposition

A total of 32 patients were included in the study. One patient was excluded because next-generation sequencing was negative for ROS1 fusion, leaving 31 patients in the study. The patient disposition diagram is illustrated in Figure 8.1. As shown, 30 patients were evaluated for PFS analyses and 29 patients were evaluated for best response according to RECIST criteria, because one patient died after one week of treatment (and was not included in the PFS analysis) and another patient died after two weeks but before tumour assessment (and was not included in the best response analysis).

Figure 8.1: Patient disposition diagram for the EUROS 1 cohort



Mazières, J. et al. J Clin Oncol. 33(9):992-999.

Summary of Outcomes

Efficacy Outcomes

Response Outcomes

During the study time, 24 patients (80 %) achieved objective responses, including five patients (16.7%) with CR and 19 patients (63.3%) with a PR. Four patients (13.3%) had disease progression during the study time, and two patients (6.7%) had SD. Disease control rate was 86.6%.

Progression-Free Survival (PFS)

In the EUROS1 cohort, the median PFS time was reported to be 9.1 months, and the PFS rate at 12 months was 44%. At the time of analysis, 18 patients were still receiving treatment. The Kaplan-Meier curve for PFS is shown in Figure 8.2.

Figure 8.2: Progression-free survival in patients with ROS1 rearrangements in the EUROS1 study

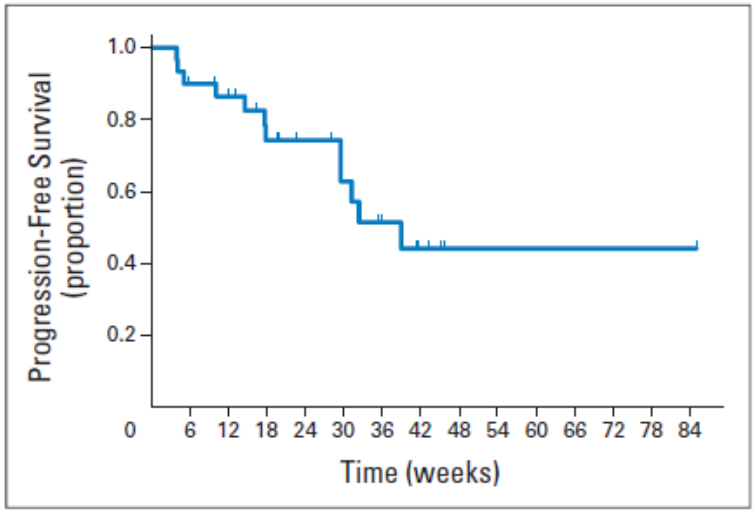


Fig 5. Progression-free survival on crizotinib in patients with lung cancer and an *ROS1* rearrangement.

Mazières, J. et al. J Clin Oncol. 33(9):992-999.

Harms Outcomes

Because this was a retrospective study, the authors of the study reports stated that monitoring safety outcomes was not possible in a prospective manner. Therefore, every investigator was asked to retrospectively declare all grade 4 and 5 AEs their patients reported while receiving crizotinib. According to Mazières et al., no unexpected AEs were observed in the EUROS1 study.

Conclusion

Mazières et al concluded that crizotinib was "highly active at treating lung cancer in patients with a ROS1 rearrangement, suggesting that patients with lung adenocarcinomas should be tested for ROS1. Prospective clinical trials with crizotinib and other ROS1 inhibitors are ongoing or planned."

9 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 (Xalkori) for ROS1- positive NSCLC. 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 CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. 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 clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials October 2018, Embase 1974 to 2018 December 05, Ovid MEDLINE(R) ALL 1946 to December 05, 2018

#	Searches	Results
1	Crizotinib/ or (crizotinib* or Xalkori* or Ksalkori* or "PF 02341066" or PF2341066 or PF02341066 or PF 2341066 or PF1066 or PF 1066 or 53AH36668S).ti,ab,ot,hw,rn,nm,kw,kf.	8787
2	Carcinoma, Non-Small-Cell Lung/	57392
3	exp Lung/ and Carcinoma, Large Cell/	435
4	(NSCLC? or LCLC?).ti,ab,kf,kw.	110046
5	((non small cell or nonsmall cell or large cell or undifferentiated) adj5 (lung or bronchial or pulmonary) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kf,kw.	154675
6	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kf,kw.	45223
7	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kf,kw.	3645
8	or/2-7	214323
9	1 and 8	5230
10	9 use medall	1350
11	9 use cctr	172
12	*crizotinib/ or *"3 [1 (2,6 dichloro 3 fluorophenyl)ethoxy] 5 [1 (4 piperidinyl) 1h pyrazol 4 yl] 2 pyridinylamine"/ or (crizotinib* or Xalkori* or Ksalkori* or "PF 02341066" or PF02341066 or PF2341066 or PF 2341066 or PF1066 or PF 1066).ti,ab,kw.	5917
13	Non small cell lung cancer/ or Large cell lung carcinoma/ or Lung adenocarcinoma/	119725
14	(NSCLC? or LCLC?).ti,ab,kw,dq.	109852
15	((non small cell or nonsmall cell or large cell or undifferentiated) adj5 (lung or bronchial or pulmonary) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab,kw,dq.	154205
16	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	45353
17	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplasm* or tumor* or tumour*)).ti,ab,kw,dq.	3638
18	or/13-17	226903
19	12 and 18	4310
20	19 use oemezd	2861
21	20 not conference abstract.pt.	1505

22	20 and conference abstract.pt.	1356
23	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.	1110134
24	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	852136
25	Multicenter Study.pt.	321774
26	Clinical Studies as Topic/	151639
27	exp Clinical Trial/ or exp Clinical Trials as Topic/ or exp "Clinical Trial (topic)"/	2713746
28	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/	487120
29	Randomization/	177037
30	Random Allocation/	193862
31	Double-Blind Method/	399061
32	Double Blind Procedure/	156037
33	Double-Blind Studies/	262057
34	Single-Blind Method/	75827
35	Single Blind Procedure/	33285
36	Single-Blind Studies/	77774
37	Placebos/	328671
38	Placebo/	327583
39	Control Groups/	111328
40	Control Group/	111236
41	Cross-Over Studies/ or Crossover Procedure/	135899
42	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4000084
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	779806
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3016
45	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.	9081465
46	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	6165778
47	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	94908
48	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	470381
49	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	185002
50	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	696769
51	allocated.ti,ab,hw.	177333
52	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	114661
53	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24993
54	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	951

55	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11144
56	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17526
57	trial.ti,kf,kw.	877120
58	or/23-57	14065647
59	exp animals/	45957972
60	exp animal experimentation/	2318297
61	exp models animal/	1733518
62	exp animal experiment/	2318297
63	nonhuman/	5635267
64	exp vertebrate/	44715265
65	animal.po.	0
66	or/59-65	47684069
67	exp humans/	37087367
68	exp human experiment/	429090
69	human.po.	0
70	or/67-69	37088807
71	66 not 70	10596173
72	58 not 71	11331889
73	10 or 11 or 21	3027
74	73 and 72	1451
75	limit 74 to english language	1377
76	remove duplicates from 75	971
77	22 and 72	859
78	limit 77 to english language	859
79	limit 78 to yr="2013 -Current"	720
80	Remove duplicates from 79	711
81	76 or 80	1682

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#14	Search **#13 AND publisher[sb]**	7
#13	Search **#1 AND #7 AND #12**	420
#12	Search **#9 OR #10 OR #11**	2522457
#11	Search **random*[tiab] OR sham[tiab] OR placebo*[tiab] OR single blind*[tiab] OR double blind*[tiab] OR triple blind*[tiab] OR control group*[tiab] OR clinical stud*[tiab] OR clinical**	1919656

Search	Query	Items found
	trial*[tiab] OR non-random*[tiab] OR non-random*[tiab] OR quasi-random*[tiab] OR quasirandom*[tiab] OR study phase*[tiab] OR trial phase*[tiab] OR crossover stud*[tiab] OR cross over stud*[tiab] OR crossover trial*[tiab] OR cross over trial*[tiab] OR multicenter stud*[tiab] OR multi center stud*[tiab] OR multi-center stud*[tiab] OR multi-center stud*[tiab] OR multicentre stud*[tiab] OR multi centre stud*[tiab] OR multi-centre stud*[tiab] OR multi-centre stud*[tiab] OR multicenter trial*[tiab] OR multi center trial*[tiab] OR multi-center trial*[tiab] OR multi-center trial*[tiab] OR multicentre trial*[tiab] OR multi centre trial*[tiab] OR multi-centre trial*[tiab] OR multi-centre trial*[tiab] OR allocated[tiab] OR openlabel stud*[tiab] OR open-label stud*[tiab] OR openlabel trial*[tiab] OR open-label trial*[tiab] OR equivalence stud*[tiab] OR equivalence trial*[tiab] OR superiority stud*[tiab] OR superiority trial*[tiab] OR non-inferiority stud*[tiab] OR noninferiority stud*[tiab] OR non-inferiority trial*[tiab] OR noninferiority trial*[tiab] OR pragmatic stud*[tiab] OR pragmatic trial*[tiab] OR practical trial*[tiab] OR quasiexperimental stud*[tiab] OR quasi experimental stud*[tiab] OR quasiexperimental trial*[tiab] OR quasi experimental trial*[tiab] OR trial[ti] OR trial[ot] OR phase 1[tiab] OR phase 2[tiab] OR phase 3[tiab] OR phase 4[tiab] OR phase 5[tiab] OR phase I[tiab] OR phase II[tiab] OR phase III[tiab] OR phase IV[tiab] OR phase v[tiab] OR phase one[tiab] OR phase two[tiab] OR phase three[tiab] OR phase four[tiab] OR phase five[tiab]	
#10	Search **Clinical Studies as Topic[mh] OR Clinical Trial[mh] OR Clinical Trials as Topic[mh] OR Multicenter Study[mh] OR Multicenter Studies as Topic[mh] OR Randomization[mh] OR Random Allocation[mh] OR Double-blind method[mh] OR double blind procedure[mh] OR double blind studies[mh] OR Single-blind method[mh] OR single-blind procedure[mh] OR Single-blind studies[mh] OR Placebos[mh] OR Placebo[mh] OR Control Groups[mh] OR Control Group[mh] OR Cross-Over studies[mh] OR Crossover Procedure[mh]**	591390
#9	Search **Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR Pragmatic Clinical Trial[pt] OR Clinical Study[pt] OR Adaptive Clinical Trial[pt] OR Equivalence Trial[pt] OR Clinical Trial[pt] OR Clinical Trial, Phase I[pt] OR Clinical Trial, Phase II[pt] OR Clinical Trial, Phase III[pt] OR Clinical Trial, Phase IV[pt] OR Multicenter Study[pt]**	991567
#8	Search **#1 AND #7 AND publisher[sb]**	51
#7	Search **#2 OR #3 OR #4 OR #5 OR #6**	86313
#6	Search **((bronchioloalveolar[tiab] OR bronchiolo alveolar[tiab]) AND (carcinoma*[tiab] OR cancer*[tiab] OR neoplasm*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab]))**	1789
#5	Search **((bronchial[tiab] OR pulmonary[tiab] OR lung[tiab]) AND (adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab]))**	33004
#4	Search **((nonsmall cell[tiab] OR non small cell[tiab] OR large cell[tiab] OR undifferentiated[tiab]) AND (lung[tiab] OR bronchial[tiab] OR pulmonary[tiab]) AND (cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab]))**	60407
#3	Search **NSCLC[tiab] OR NSCLCs[tiab] OR LCLC[tiab] OR LCLCs[tiab]**	36116
#2	Search **"Carcinoma, Non-Small-Cell Lung"[Mesh]**	46148
#1	Search **Crizotinib[mh] OR crizotinib [Supplementary Concept] OR Crizotinib[tiab] OR Xalkori[tiab] OR Ksalkori*[tiab] OR PF 02341066[tiab] OR PF2341066[tiab] OR PF02341066[tiab] OR PF 2341066[tiab] OR PF1066[tiab] OR PF 1066[tiab] OR 53AH36668S[rn]**	1931

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

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

World Health Organzation
http://apps.who.int/trialsearch/

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

Search: Xalkori / crizotinib, NSCLC

Select international agencies including:

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

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

Search: Xalkori / crizotinib, NSCLC

Conference abstracts:

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

European Society for Medical Oncology
https://www.esmo.org/

Search: Xalkori / crizotinib, NSCLC – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2018Dec 5) with in-process records & daily updates via Ovid; Embase (1974-2018Dec 5) via Ovid; The Cochrane Central Register of Controlled Trials (October 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were crizotinib, Xalkori and non-small cell lung cancer.

Methodological filters were applied to limit retrieval to all types of clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of April 4, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. 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.

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.

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.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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