pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lorlatinib (Lorbrena) for Non-Small Cell Lung Cancer

January 30, 2020

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TABLE OF CONTENTS

List of Abbreviations

AE(s)	Adverse Events
CI	Confidence interval
CGP	Clinical Guidance Panel
CR	Complete Response
DOR	Duration of Response
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICR	Independent Central Review
NSCLC	non small cell lung cancer
NR	Not reached
ORR	Objective response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression free survival
PR	Partial Response
TTP	Time to tumour progression

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 lorlatinib for non-small cell lung cancer (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 lorlatinib for NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient 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 Group Input on lorlatinib for NSCLC, a summary of submitted Provincial Advisory Group Input on lorlatinib for NSCLC, and a summary of submitted Registered Clinician Input on lorlatinib for 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 effect of lorlatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

The reimbursement request is for the treatment of adult patients ALK-positive metastatic NSCLC who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib. On February 22, 2019, Health Canada issued a notice of compliance with conditions (NOC/c – to provide confirmatory trial results of an ongoing, Phase 3, randomized, open-label trial comparing the safety and efficacy of lorlatinib to crizotinib in the first-line treatment of subjects with advanced ALK+ NSCLC and provide post market safety monitoring studies); the Health Canada indication aligns with the reimbursement request. [1]

According to the Health Canada Product Monograph, the recommended dose of lorlatinib is 100 mg taken orally once daily continuously. As stated in the Health Canada Product Monograph, treatment with lorlatinib is to be continued as long as the patient is deriving clinical benefit from therapy. [1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One non-randomized, phase II, ongoing, multicentre, open-label, single-arm study (Trial 1001) met the inclusion criteria. The aim of this study was to investigate the activity of single-agent lorlatinib in patients with ALK-positive, advanced, NSCLC.[2] This study was funded by Pfizer. All authors, some employed by Pfizer contributed towards the interpretation of the data as well as the development and approval of the manuscript. Complete access to the data was available to all study authors and the corresponding author had authority to submit the publication.

The primary endpoint of Trial 1001 was objective response rate by independent central review and intracranial objective response rate. Key secondary outcomes included

duration of response (DOR) by independent central review, progression free survival (PFS) by independent central review and overall survival (OS).

Trial 1001 enrolled 276 patients between September 15, 2015 and October 3, 2016 across 47 centres from 14 countries which included Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Singapore, Spain, Switzerland, Taiwan, and United States (US). [3] [4] Randomization was not performed. Patients were treated with 100 mg of lorlatinib once daily and the ALK positive patients were placed in one of the following cohorts: EXP 1 - treatment naïve (n=30), EXP 2 - prior crizotinib only (n=27), EXP 3A - prior crizotinib plus chemotherapy (n=32) or EXP 3B - one second generation ALK TKI ± chemotherapy (n=28), EXP 4 - two prior ALK TKIs± chemotherapy (n=65), EXP 5 - three prior ALK TKIs± chemotherapy (n=46); ROS 1 positive patients were placed in the EXP6 cohort - any line of treatment (n=47). The following cohorts: EXP 3B, EXP 4 and EXP 5 are of interest for this review as the population aligns with the reimbursement indication. Results for these cohorts will be reported. A pooled analysis for safety (cohorts EXP 1-6 and EXP 3B-5) as well as quality of life for cohorts EXP 3B-5 was reported. The March 15, 2017 data cut off represents the actual study completion date. According to the sponsor, the February 2, 2018 data cut off reflects ad-hoc updated analyses.

Among 276 patients, there were a total of 7 patients from Canada.[5] The ITT population comprised of EXP 3B, EXP 4-5 included 139 patients of which 41 patients remained on lorlatinib treatment and 98 patients discontinued treatment.[3] The following are reasons for exclusions: objective progression or relapse (n=66), adverse events (AEs) (n=12), patient no longer willing to participate in the study (n=6), global deterioriation of health status (n=6), patient died (n=5), protocol violation (n=1), other (n=2). [3]

The median age of patients in EXP3B and EXP4-5 were 54 years old and 51 years old respectively. The proportion of female patients was 57% in EXP 3B and 56% EXP 4-5. The majority of patients were white (25%) or of Asian race (57%) in EXP 3B compared to 53% white and 33% Asian race in the EXP 4-5. An ECOG PS of 0 and 1 was reported in 54% and 46% of patients respectively in EXP 3B. In EXP 4-5, an ECOG PS of 0 and 1 was reported in 41% and 53% of patients respectively. There were 13 patients (46%) in EXP 3B and 83 patients (75%) in EXP 4-5 with brain metastases present at baseline. All 28 patients (100%) in the EXP 3B cohort received one previous ALK TKI regimen. In EXP 4-5, 65 patients (59%) received two previous ALK TKI regimens whereas 42 patients (38%) received 3 prior ALK TKI regimens. Lorlatinib was administered orally in a tablet form beginning with a dose of 100 mg once daily continuously in 21-day cycles. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients could continue treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion.

Efficacy Outcomes

The key efficacy outcomes of Trial 1001 are summarized in Table 1.

Table 1: Highlights of Key Outcomes

	Data cut-off date: March 15, 2017		**Data cut-off date: February 2, 2018**	
	EXP 3B	**EXP 4-5**	**EXP 3B**	**EXP 4-5**
Median follow-up months, for response (95% CI)	7.0 months (5.6-12.7)[2]	7.2 months (6.9-7.2)[2]	not reported	9.9 months[3]

Primary Outcome				
Confirmed ORR by ICR(%, 95% CI)	9 (32.1%; 15.9-52.4)[2]	43 (38.7%; 29.6-48.5)[2]	12 (42.9%; 24.5-62.8)[3]	44 (39.6%; 30.5-49.4)[3]
Confirmed Intracranial ORR by ICR (%, 95% CI)	5 (55.6%; 21.2-86.3)[2]	26 (53.1%; 38.3-67.5)[2]	6 (66.7%; 29.9-92.5)[3]	25 (52.1%; 37.2-66.7)[3]
Secondary Outcomes				
Median time to tumour response, months[3]	1.4 (1.3-3.0)	1.4 (1.2-9.9)	1.4 (1.2-16.6)	1.4 (1.2-16.4)
Median time to first Intracranial response, months [3]	1.4 (1.3-3.0)	1.4 (1.2-6.2)	1.4 (1.2-3.0)	1.4 (1.2-16.2)
Median duration of response by ICR, months (95% CI)[3]	NR (4.1-NR)	NR (5.5-NR)	5.6 (4.2-NR)	9.9 (5.7-24.4)
Median duration of Intracranial response by ICR, months (95% CI) [3]	NR (4.1-NR)	14.5 (6.9-14.5)	NR (4.1-NR)	12.4 (6.0-NR)
Median PFS by ICR, months (95% CI) [3]	5.5 (2.9-9.0)	6.9 (5.4-9.5)	5.5 (2.9-8.2)	6.9 (5.4-9.5)
PFS				
12 months % (95% CI) [3]	29.3% (11.9-49.3)	31.9% (21.2-43.1)	27.3% (12.2-45.0)	33.3% (24.2-42.6)
18 months %(95% CI) [3]	not reported	not reported	21.9% (8.1-39.9)	23.1% (15.2-32.0)
Median OS months	NR [4]	NR [4]	21.1 (12.3-NR)[3]	19.2 (15.4-NR)[3]
OS				
12 months % (95% CI)[3]	not reported	not reported	69.8% (48.5- 83.6)	67.3% (57.6- 75.4)
18 months % (95% CI)[3]	not reported	not reported	61.6% (40.2-77.2)	54.2% (44.0-63.2)

CI = confidence interval, **NR** = not reached, **ORR**=Objective Response Rate, **PFS**=Progression Free Survival, **OS**=Overall Survival, DOR=Duration of Response, IC=Intracranial, ICR=Independent Central Review

Primary Outcomes

Objective Response Rate (ORR)-Independent Central Review

At the data cut off-of March 15, 2017, the median duration of follow-up was 7.0 months (95% confidence interval [CI] 5.6-12.7) in EXP 3B and 7.2 months (95% CI 6.9-7.2) in EXP 4-5, respectively. [2] There were 9 patients (32.1%, 95% CI 15.9-52.4) and 43 patients (38.7%, 95% CI 29.6-48.5) had a confirmed ORR in EXP 3B and EXP4-5 respectively.[2] One patient (3.7%) in EXP 3B and two patients (1.8%) in EXP 4-5 had a complete response (CR).[3] Eight patients (29.6%) in EXP 3B and 41 patients (36.9%) in EXP 4-5 had a PR. At the data cut-off of February 2, 2018, the median follow-up was 9.9 months (EXP 4-5).[3] The ORR was slightly higher in EXP 3B, EXP 4 and EXP 5.[3]

Intracranial Objective Response Rate (ORR)- Independent Central Review

At the data cut-off March 15, 2017 for intracranial ORRs, 5 patients (55.6%), 95% CI 21.2-86.3 and 26 patients (53.1%), 95% CI 38.3-67.5 had a confirmed ORR in EXP 3B and EXP 4-5 respectively.[3] One patient (11.1%) in EXP 3B and 10 patients (20.4%) in EXP 4-5 had a CR. Four patients (44.4%) in EXP 3B and 16 patients (32.7%) in EXP 4-5 had a PR.[3]

At the data cut off-of February 2, 2018 for intracranial ORRs, the confirmed ORR was higher in EXP 3B and similar in EXP 4-5 respectively.[3]

Secondary Outcomes

Duration of Response (DOR)-Independent Central Review

At the March 15, 2017 data cut-off, the median duration of response was not reached in either the EXP 3B (95% CI 4.1, NR) and EXP 4-5 (95% CI 5.5-NR) cohorts.[3] The median duration of intracranial response was not reached (95% CI 4.1-NR) in EXP 3B and 14.5 months (95% CI 6.9-14.5) in EXP 4-5.

At the February 2, 2018 data cut-off, the median duration of response was 5.6 months (95% CI 4.2-NR) in EXP 3B and 9.9 months (5.7-24.4 months) in EXP 4-5. The median duration of intracranial response was consistent with the March 15, 2017 data cut off in EXP 3B and 12.4 months (95% CI 6.0-NR) in EXP 4-5. [3]

Time to tumour response (TTR)-ITT population

At the March 15, 2017 data cut-off, the median TTR was 1.4 months (1.3-3.0) and 1.4 months (1.2-9.9) in EXP 3B and EXP 4-5, respectively. The median intracranial TTR was 1.4 months (1.3-3.0) and 1.4 months (1.2-6.2) in EXP 3B and EXP 4-5, respectively.

At the February 2, 2018 data cut-off, the results were consistent with the March 15, 2017 data cut-off.

Progression Free Survival (PFS)-Independent Central Review

At the data cut-off March 15, 2017, the median PFS was 5.5 months (95% CI 2.9-9.0) in the EXP 3B and 6.9 months (95% CI 5.4-9.5) in EXP 4-5. There were ten patients (37.0%) censored in EXP 3B and 49 patients (44.1%) censored in EXP 4-5. The event free survival at 12 months was 29.3% (95% CI 11.9-49.3) and 31.9% (95% CI 21.2-43.1) in EXP 3B and EXP 4-5 respectively.[3]

At the data cut-off of February 2, 2018, the median PFS was consistent with the March 15, 2017 data cut off. There were 8 patients (28.6%) censored in EXP 3B and 34 patients (30.6%) censored in EXP 4-5. The event free survival at 12 months was consistent with the March 15, 2017 data cut off. At 18 months, the event free survival was 21.9% (95% CI 8.1-39.9) and 23.1% (95% CI 15.2-32.0) in EXP 3B and EXP 4-5 respectively.[3]

Overall Survival (OS)

At the data cut-off of February 2, 2018, the median duration of follow-up for OS was approximately 20 months for EXP 3B-5. Among patients in EXP3B and EXP 4-5, the median OS reached 21.1 months (95% CI: 12.3- NR) and 19.2 months (95% CI: 15.4- NR),

respectively. For EXP 3B, 60.7% patients were still censored for OS. The OS for EXP 3B at 12 months was 69.8% (95% CI: 48.5- 83.6) and the OS at 18 months was 61.6% (95% CI: 40.2- 77.2). For EXP 4-5, a total of 55 (49.5%) patients were censored for OS. The OS for EXP 4-5 at 12 months was 67.3% (95% CI: 57.6- 75.4) and the OS at 18 months was 54.2% (95% CI: 44.0- 63.2).[3]

Time to Tumour Progression (TTP)

Based on independent assessment, the median TTP was 11 months (95% CI: 8.2- 13.7) overall. In cohort EXP-3, TTP was 9.0 months (95% CI: 5.5, NR), 8.4 months for cohort EXP 4 (95% CI: 5.6-13.7), and 7.1 months (95% CI: 4.1- 12.5) for cohort EXP 5.[3]

The median intracranial TTP was not reached for cohort EXP 3 and EXP 5 and 15.7 months (95%CI: 11.0- 15.7) for cohort EXP-4.

Patient Reported Outcomes (PROs)

At the data cut-off of March 15, 2017, there were 128 ALK-positive patients in the pooled EXP 3B-EXP 5 cohort out of 275 patients evaluable for PROs. A questionnaire was deemed complete provided at least one question was answered.[4] The EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were administered at each cycle up to 24 cycles. According to the safety analysis set of 275 patients (EXP 1-6), in EXP 4, the completion rates ranged from approximately 95% in cycle 1 to 100% in cycle 25. Similarly, in EXP 5, the completion rates ranged from approximately 96% in cycle 1 to 100% in cycle 25.[6] Completion rates were not available for EXP 3B.

Improved was defined as a ≥10-point increase from baseline and worse was defined as a ≥10-point decrease from baseline. Stable was defined as a patient who neither improved nor worsened.[4] The results showed that from baseline, 49 patients (38.3%) demonstrated improvement on the global QoL EORTC QLQ- C30, 49 patients (38.3%) were stable and 30 patients (23.4%) demonstrated worsening symptoms.

On the EORTC QLQ-C30 the highest improvement from baseline was observed for role functioning among 50 patients (39.1%) followed by 33.6% of patients for emotional functioning. From baseline, 74 patients (57.8%) of patients showed stable cognitive function whereas 47 patients (25.5%) demonstrated worse cognitive functioning.

Across the symptom scales of the EORTC QLQ-C30, from baseline, the highest improvement was for fatigue among 62 patients (48.4%) followed insomnia and appetite loss among 59 patients (46.1%) for each scale. From baseline, nausea and vomiting was stable among 86 patients (67.2%), diarrhea (65.6%) for 84 patients and constipation (61.7%) for 79 patients. From baseline, a worsening of symptoms was observed for dyspnea (23.4%).

On the QLQ-LC13 symptoms scale, the highest improvement from baseline observed for cough among 53 patients (41.4%), 41 patients (32.0%) for pain in other parts and dyspnea among 39 patients (30.5%). From baseline, haemoptysis was stable among 109 patients (85.2%) and dysphagia (78.9%) for 101 patients. From baseline, while peripheral neuropathy was stable among 67 patients (52.3%), there was a worsening in symptoms among 48 patients (37.5%).

Safety Outcomes

At the March 15, 2017 data cut-off, in the safety analysis set of 275 patients, patients received 100 mg QD in 21-day cycles. Hypercholesterolemia was the most common treatment related adverse event that occurred in 224 patients (81%) followed by hypertriglyceridemia among 166 patients (60%), oedema in 119 patients (43%) and peripheral neuropathy among 82 patients (30%). The most commonly reported Grade 3-4 treatment related adverse event was hypercholesterolemia and hypertriglyceridemia which occurred in 43 patients (16%) each. Serious treatment-related adverse events across all grades occurred in 19 (7%) of 275 patients. Cognitive effects were the most common serious treatment related adverse event which occurred in 2 patients (0.7%). There were 7 patients (3%) that discontinued due to treatment-related adverse events. Reasons for permanent discontinuation from the study included affect lability, cognitive disorder, confusional state, hallucination (auditory/visual), hydrocephalus, leukocytosis, pneumonitis and tinnitus. [5] There were no treatment related deaths.[2]

In the pooled EXP 3B-5 cohort (data cut-off February 2, 2018), any Grade 3 and Grade 4 adverse event was reported in 51 patients (36.7%) and 9 patients (6.5%) respectively. The most common Grade 3 and Grade 4 adverse event was hypercholesterolemia which occurred in 19 patients (13.7%) and 1 patient (0.7%) respectively. In addition, Grade 3 and Grade 4 hypertriglyceridemia was observed in 20 patients (14.4%) and 5 patients (3.6%) respectively. These adverse events were managed with lipid-lowered agents and dose modifications.[7]

Treatment-related adverse events due to dose interruptions and dose reductions occurred in 83 patients (30%) and 61 patients (22%) of 275 patients, respectively. Specifically, the most common treatment-related cause for dose interruptions and dose modifications was oedema which occurred in 16 patients (6%) and 18 patients (7%) of 275 patients, respectively. [2]

Limitations

Although this phase II trial is comprised of several cohorts (EXP 1-6), only EXP 3B-5 is of interest for this review.

- A pooled analysis plan for EXP 3B-5 was not outlined a priori in the protocol. In addition, according to the trial publication, the sample size of each cohort was based on an estimation design with no specific hypothesis testing.[2] The sponsor noted that when the study first started, data were available only for activity of other ALK TKIs after crizotinib, not for the other cohorts that the sponsor tested; thus, the study was based on a simple estimation design to evaluate activity of lorlatinib in the different prior treatment settings. EXP 3B, EXP 4 and EXP 5 was not powered to detect statistical significance for the primary and secondary endpoints [7] Therefore, the interpretation of these results is limited.
- Moreover, a single arm clinical trial was conducted, thus, comparative effectiveness cannot be assessed.
- Methods for testing for multiplicity were not outlined in the protocol for primary and secondary endpoints.
- Results related to patient-reported outcomes were descriptive only. It is unclear the characteristics of patients that did not complete the EORTC QLQ C30 at baseline and whether these patients may have responded differently to patients that did complete the questionnaire. Approximately 20% of major protocol

deviations were attributed to inclusion criteria which suggests a possible selection bias and implications on sample sizes of the cohorts.

The sponsor provided feedback on the pERC Initial Recommendation and disagreed with the interpretation that the results of Trial 1001 are only hypothesis generating. The sponsor stated that the EXP 3B-5 cohorts had the robustness to justify lorlatinib's conditional approval from Health Canada. In response to the sponsor's feedback, the Methods team confirmed that the trial publication stated that the sample size of each cohort was based on an estimation design with no specific hypothesis testing.[2] The sponsor clarified at the Checkpoint meeting that when the study first started, data were available only for activity of other ALK TKIs after crizotinib, not for the other cohorts that the sponsor tested; thus, the study was based on a simple estimation design to evaluate activity of lorlatinib in the different prior treatment settings. Therefore, the sample size of EXP 3B, EXP4 and EXP5 was not powered to detect statistical significance for the primary and secondary endpoints.[7]

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

From a patient's perspective, outcomes that need to be addressed include: to stop or slow the progression of disease, reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy. Patients and caregivers value quality of life and independence as treatment outcomes. Patients would like more treatment options and would be willing to try additional or combination treatments if the side effects were no worse than their current treatment.

Provincial Advisory Group (PAG) Input

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

Clinical factors:
- Eligible patient population
- Comparative data to brigatinib, ceritinib as well as alectinib

Economic factors:
- Pricing structure of lorlatinib

Registered Clinician Input

Two joint registered clinician input submissions were provided, representing a total of 9 clinicians. One joint submission on behalf of seven clinicians (one oncologist, 6 unspecified) were from Lung Cancer Canada (LCC) as well as one joint submission on behalf of 2 clinicians from Cancer Care Ontario Lung Drug Advisory Committee were received for the review of lorlatinib as monotherapy for ALK-positive metastatic NSCLC who have progressed on crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

Clinicians consider access to multiple lines of ALK directed therapy to be valuable for ALK-positive patients as there is an unmet need for these patients. Access to new therapies

translates directly into improved overall survival outcomes. The primary benefit of lorlatinib is that it acts as an additional line of therapy before chemotherapy for this indication. It does not replace any current treatments. Compared to lorlatinib, other treatment options (chemotherapy, immunotherapy) offer limited benefit and greater toxicity. Clinicians find the eligibility criteria for the phase II trial applicable to clinical practice. In treatment sequence, lorlatinib should follow use of a next generation ALK inhibitor. Clinicians did not find conclusive evidence to support the number of ALK inhibitors a patient should receive in their treatment trajectory. Companion testing is not required for lorlatinib.

LCC added an additional consideration: Past pCODR submissions and clinical experience have demonstrated remarkable consistency between phase II and phase III targeted therapy clinical trial results. Therefore, they suggest that the positive results in the phase II trial prove lorlatinib's potential. They caution that a delayed positive recommendation means unnecessary delays in patient access.

Summary of Supplemental Questions

In the absence of data on the comparative efficacy of lorlatinib compared to other available treatments in second-line or later ALK-positive advanced NSCLC, the sponsor undertook an indirect treatment comparison (ITC) in the form of an unanchored matched-adjusted indirect comparison (MAIC) in order to evaluate overall survival and progression-free survival[8] and inform a cost-effectiveness model relevant to the economic evaluation of this report. [9] The objective of this section is to summarize and critically appraise the sponsor-submitted unanchored MAIC comparing lorlatinib with chemotherapy for the treatment of ALK-positive NSCLC. Data from this unanchored MAIC was used in the pharmacoeconomic model comparing lorlatinib with chemotherapy. In the economic model, the assumption was made that the relative efficacy of lorlatinib versus pemetrexed or docetaxel monotherapy is similar to the combination of pemetrexed-platinum. The unanchored MAIC does not include combination of pemetrexed-platinum, rather the economic model assumes relative efficacy of lorlatinib versus pemetrexed or docetaxel monotherapy (from the MAIC) is similar to combination of pemetrexed-platinum. [9]

See Section 7.1 for more information.

The objective in this section is to summarize and critically appraise the published systematic review and meta-analysis by Wao et al. [10] in which overall survival is estimated in lung cancer patients when no anticancer therapy is provided. The CGP identified BSC as a relevant comparator. In the absence of a head to head trial comparing lorlatinib to BSC and due to the limited ability to conduct an ITC, the sponsor proposed to match survival outcomes to those reported in this published systematic review.

See Section 7.2 for more information.

Comparison with Other Literature

The sponsor provided real world evidence (RWE) described below. Based on consultation with members of CGP, selection criteria for the review were developed and outlined in the protocol (see Section 6.2.1). Thus, these RWE studies did not meet the a priori study design criteria outlined in Section 6: Systematic Review.

1. The French nominative Temporary Authorization of Use (nATU) is a non-randomized observational study that included 336 patients treated with lorlatinib across 140 centers. The sponsor noted that the study involved no formal protocol, statistical analysis plan,

data monitoring, or case report form were in place for collection or analysis of these data.[7]

2. Similarly, a non randomized study was conducted at a single institution in Austria that included 32 NSCLC patients previously treated with various chemotherapies and TKIs that received treatment with lorlatinib (100mg daily p.o.) in an pre-approval access program between June 2016 and April 2019.[11] Due to the small sample size and study conducted at a single site, this limits the external validity of the results to the broader target population.

In Turkey, a single-arm, open-label, multicenter early access program was available across 27 oncology centres between February 2017 and December 2018. Ninety-one patients received treatment with lorlatinib (100 mg p.o/day) if they had advanced stage *ALK*- or *ROS1*-positive NSCLC and had progressed on crizotinib and/or second generation ALK inhibitors such as ceritinib or alectinib.[12] As the study was open-label, investigators and patients were not blinded to the treatment patients received and may impact the internal validity of the results.

Based on the aforementioned methodological limitations, the evidence from these RWE studies are not robust. Therefore, conclusions on the safety and efficacy of lorlatinib cannot be made.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence.

Table 2: Assessment of generalizability of evidence for Lorlatinib for NSCLC

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	Patients were included in E3B-5 had ECOG status of 0 - 2.[2] ECOG score, n (%) / EXP 3B / EXP 4-5 0 / 15 (54) / 46 (41) 1 / 13 (46) / 59 (53) 2 / 0 / 6 (5)	Are the trial results generalizable to patients with an ECOG score of >2?	CGP agreed that trial results can be generalized to patients with an ECOG performance status of three. CGP acknowledged that if a patient with an ECOG performance status of four were fit enough to be prescribed a TKI from a physician, this would be a rare occurrence and would take place in the naïve setting, not in the same setting as lorlatinib.
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary Outcomes[2] -Objective tumour response -Intracranial tumour response Secondary Outcomes[2] -Duration of Response - Intracranial duration of response - Time to first tumour response -Time to tumor progression -PFS -OS -Safety -Patient-reported Outcomes	Are the outcomes assessed in the trial appropriate and are these outcomes the most important to clinicians?	The CGP agreed that objective tumour response and intracranial tumour response were appropriate primary endpoints for a phase II study. CGP noted that the secondary endpoints such as overall survival, safety, and quality of life are important outcomes for clinicians. Outcomes such as intracranial duration of response and duration of response are appreciated by clinicians.
Setting	Supportive Medications	There were 64/65 patients (98.5%) and 46 patients (100%) in EXP 4 and EXP 5 respectively that received concomitant medications. The most frequently used concomitant drugs (used by >30 patients) were atorvastatin, dexamethasone, fenofibrate, furosemide,	Are the results of the trial generalizable to a setting where different concomitant medications in patients are used in Ontario? Across Canada?	Yes, to both.

		ibuprofen, lorazepam, omeprazole, paracetamol, potassium chloride, pravastatin, pravastatin sodium, prednisone, rosuvastatin, rosuvastatin calcium, and sennoside A+B. It is unclear the proportion of EXP 3B that received concomitant medications.[6]		

1.2.4 Interpretation

Lorlatinib, as a treatment for ALK positive non-small cell cancer originating in lung was studied in a prospective multi-centre, multi-country, phase II trial in multiple clinically relevant populations – *Phase I/II Study of PF-06463922 (an ALK/ROS Tyrosine Kinase Inhibitor) in patients with advanced non-small cell lung cancer harbouring specific molecular alterations (NCT01970865*).[13] The cohorts of interest to clinical practice made up the current submission, and were reviewed by the Methods team include those in arms 3B (one 2nd generation ALK TKI +/- chemotherapy), and EXP 4 and 5 (two and three prior ALK TKI's +/-chemotherapy). The total number of patients in these cohorts was 139. Of these patients, approximately 70% (96/139) had intracranial disease. This matches the need in clinical practice for patients who have progressed after alectinib therapy or other post-crizotinib TKI's.

The primary endpoints of the study were imaging endpoints :response rate and intracranial response rate. At the most recent data-cut-off (February 2, 2018),[3] the response rates were approximately 40%, the intracranial response approximately 50%. The median progression free survival was 5.5 months in EXP 3B, and 6.9 months in EXP 4 and 5. The corresponding event free survival rates (free of death or progression) at 12 months was 27% and 33.3%, and at 18 months 22% and 23% respectively. The median overall survival was approximately 20 months. At 18 months, 54% of patients in EXP 4/5 were alive, while 62% in EXP 3B were alive.

A cross-trial comparison, using advanced cross-trial comparison techniques such as Matched Adjusted Indirect Comparison (MAIC)was used in order to try to answer the question of how these outcomes may compare to standard therapy. [8] A meta-analysis of outcomes/survival with no treatment in advanced lung cancer was used in order to attempt to understand outcomes in this specific patient population if no treatment were provided.[10]

The meta-analysis of outcomes with no treatments was reviewed by the Methods team to have good internal validity, but the CGP considers this to have little external validity to this specific subtype of driver-mutation (i.e., ALK) cancer originating in lung. ALK positive cancer originating in lung is a different cancer than all-comer non-small cell lung cancer, with significantly more brain metastases in ALK positive disease, in different patient population (younger, more women, non-smoking related), at a different time in disease (untreated versus after previous treatments), and at a different time of medical care, with

changes to supportive care and other anti-cancer therapies such as radiation therapy. Smaller institutional studies have reported fairly short survival after stopping ALK-TKI therapy, but these often have significant methodologic flaws and little internal validity.

The MAIC had a reasonable framework. ALK positive patients who were in the chemotherapy arm of prior ALK-inhibitor versus Chemotherapy trials, such as the ALUR study. Caveats here however are that the trials cited, ALUR and ASCEND-5, compared alectinib and ceritinib respectively to pemetrexed or docetaxel, but all patients had previously received the most effective chemotherapy (doublet platinum chemotherapy), whereas the current request and cohorts in the current study did not/do not mandate prior platinum based chemotherapy. The comparison used would bias the treatment in favour of lorlatinib and against chemotherapy. In the matched adjusted cross-trial comparison, lorlatinib seemed to confer a very significant reduction in comparison to single agent chemotherapy in terms of progression-free survival. In clinical practice, this would align with some patients who were previously treated with platinum-doublet chemotherapy, but even if the comparator were doublet chemotherapy (instead of single agent), there would still likely be a benefit for lorlatinib, albeit of somewhat less magnitude.

A further, minor concern with the comparison is the assumption that the comparator for these patients would be chemotherapy or best supportive care. While the eligibility criteria for the trial was "disease progression on prior ALK therapy", it is also acknowledged in the trial that ALK inhibitor therapy is often continued after disease progression, usually due to radiation of oligo-progressive disease. It is unclear whether some of these patients may have been enrolled in a phase II trial, given they would have been guaranteed to receive continued ALK inhibitor even though in the absence of a trial they may have continued on their previous ALK inhibitor and received local modality therapy for oligometastatic treatment. Indeed, in the current trial the difference between PFS and OS would suggest significant post-progression survival, likely either due to treatment past progression or very good post progression supportive care and/or treatments. This is a minor concern as the likely difference in pricing between lorlatinib and other second-generation ALK inhibitors is likely to be low, so it is unlikely to meaningfully impact cost-effectiveness.

In total, the clinical guidance panel believes the following, but acknowledges that the evidence base is limited.

Effectiveness

Lorlatinib is a drug with some efficacy in ALK-positive carcinoma of the lung, and a potential significant health benefit in patients with ALK positive carcinoma of the lung. The response rate of 40% and intracranial response of 50%, coupled with the median duration of response of over 14 months, suggests that this drug does have the potential for a positive impact on ALK positive lung cancer patients' health. [3] The intracranial response rate is particularly important, as progression of intracranial disease can be a devastating outcome – leading to significant cognitive decline, significant neurological debility, and other comorbidities prior to death. Central nervous system (CNS) progression particularly is a meaningful clinical endpoint in this population, and delaying progression/improving control will improve morbidity and quality of life.

With only a single arm, multiple –cohort, phase I/II trial, with primary endpoints of response rate and intracranial response rate, there will always be some increased uncertainty regarding how this treatment would fare in a randomized clinical trial or in clinical practice, and how it would compare with other therapies (doublet chemotherapy).

The clinician input and patient input suggests that this may not be felt to be ethical or feasible to pursue, although randomized studies have been done in similar space in the past (such as the aforementioned ALUR and ASCEND-5 trials). [14,15] However, the ALUR and ASCEND-5 studies, as were the initial PROFILE 1014 studies, [14,15, 16] were largely not answering whether the tyrosine kinase inhibitor's involved should be used in patients' treatment, but rather when to use them in treatment. All trials in this patient population have a significant amount of crossover built in. If a phase III trial of lorlatinib versus doublet chemotherapy were conducted, it would necessarily have cross-over to lorlatinib from doublet chemotherapy – as did the ALUR and ASCEND-5 studies[14,15] comparing TKI's to chemotherapy - and would be answering a sequencing question –whether lorlatinib should ideally be given prior to doublet chemotherapy or following doublet chemotherapy, as there may be some equipoise here. It would not answer whether lorlatinib should be offered at all, and the CGP agrees that a placebo-controlled study would be unethical and non-feasible. Lorlatinib clearly has some benefit to some patients, but the magnitude of benefit is difficult to assess without a placebo controlled clinical trial, and the timing is difficult to assess without a randomized phase III trial comparing lorlatinib with platinum doublet chemotherapy, thus an RCT may be feasible. Although Lung Cancer Canada mentions that this type of trial would not be feasible, CGP acknowledge that it was ethical and feasible for alectinib, ceritinib, and crizotinib in similar patient populations.

In the original studies in ALK positive patients who had not received prior doublet chemotherapy (the PROFILE 1014 trial – crizotinib vs platinum doublet chemotherapy), platinum-pemetrexed showed a response rate of 45%, with a median PFS of 7 months. However, CNS response rates were not reported. In the second line setting, with docetaxel or pemetrexed as the chemotherapy comparator, intracranial response rates were 0%, and response rates were 2% for docetaxel. All of these patients had previous doublet chemotherapy. It is difficult to determine what the response rate and PFS for doublet chemotherapy is in the post-ALK-TKI setting, but it can be assumed that that it likely is substantially better than the arms in ALUR and ASCEND-5, and somewhat less than the platinum-pemetrexed arm in Profile 1014. [14,15, 16]

As lorlatinib is being requested as an additional line of therapy, and not as a replacement for therapy (i.e. doublet chemotherapy), the potential health impact of the drug to be assessed is the potential impact on mortality, morbidity, and quality of life, for the option of the addition of lorlatinib after treatment with crizotinib, a second generation ALK inhibitor and progressed; or patients who receive alectinib or ceritinib and subsequently progressed. It cannot be answered without a sequencing trial as to whether lorlatinib prior to doublet chemotherapy or lorlatinib after doublet chemotherapy is the most appropriate timing. However, it can be reasonably inferred from Trial 1001's phase II results of response rate and particularly intracranial response rate that there is likely to be a benefit for patients to have access to this drug at some point after second-generation ALK inhibitor failure. In practice and in implementation, lorlatinib would likely be used prior to doublet platinum chemotherapy in some patients, after doublet platinum chemotherapy in others, and in patients who would not ever receive or accept doublet platinum chemotherapy – similar to the patients enrolled in the clinical trial.

In terms of effectiveness, true benefit in overall survival, symptoms, or quality of life, the CGP believes it can reasonably be inferred that lorlatinib will provide a modest benefit in this rare pre-treated population of patients. It is likely, but unproven, that this will translate into a benefit in overall survival for a subset of patients with ALK-positive lung cancer, given the response rates of 40% and the prolonged duration of response (>14 months). Again, there is some uncertainty as neither of these are proven surrogates for overall survival in lung cancer, particularly response rate. These levels of response and

disease control are much higher than expected with no additional lines of therapy, or with second line single agent chemotherapy. In addition, intracranial response and control is significantly beneficial to patients even in the absence of prolonged life, given the potential consequences of intracranial progression of disease.

Quality of Life

Quality of life assessments and comparisons are particularly difficult to evaluate in a non-randomized trial, as it is expected that while quality of life may improve for patients with symptomatic disease that respond to treatment, it is also true that for patients with disease that is only mildly symptomatic, or that doesn't respond to treatment, there may be a worsening quality of life if the side effects of the medication are significant. In this trial, quality of life appeared to improve for some patients over time and decrease for some patients over time. However, it is uncertain how this compares with either chemotherapy or best supportive care. While lorlatinib is associated with a tumour responses, it also is associated with some adverse events that do impact quality of life, such as fatigue, cognitive changes, peripheral neuropathy, and weight gain. The Lung Cancer Canada report from solicited patient experiences suggested that they seemed to tolerate the drug relatively well, however, this sample of patients may be biased towards those who had benefited and tolerated the drug the best. Given the greater CNS penetration of lorlatinib, more research is required as to the etiology and proper treatment of 'cognitive changes'.

Safety

For safety, lorlatinib appeared to be safe which historically has been one of the most important outcomes of a phase II trial. Serious treatment related adverse events were rare (7%), and the majority of grade 3/4 events were biochemical abnormalities only (hyperlipidemia/hypertriglyceridemia). It is expected with increased recognition and early management, these will be manageable toxicities. Weight gain in this setting has not been reported before, and while it needs attention, it does not appear to affect safety. As there are some drug interactions however, attention will need to be placed on appropriate management of toxicities and polypharmacy. Given the low rate of withdrawal due to adverse events (3%), it appears that the drug is actually fairly tolerable, despite the side-effects noted.

Burden of Illness/Need

ALK positive cancer originating in the lung is a devastating form of a devastating cancer. Indeed, the lack of the ability to prevent this disease through lifestyle factors, the lack of known modifiable risk factors, and the high predilection for CNS metastases, combine to make this a disease significantly different than lung cancer. This is a therapy expected to apply to a small percentage of patients with cancer beginning in the lung, and as a third or second line therapy will be reserved for approximately 100-200 patients per year in Canada (~28 600 new cases X 0.85 NSCLC X 0.71 Non-Squamous X 0.02 ALK positive X 0.7 metastatic (stage IV at presentation or developed metastatic disease X 0.6 on third line = 142). There is a need for additional lines of therapy to be given for patients progressing on standard therapies.

Patients and clinicians clearly value the oral option for treatment. Patients who have received other oral TKI's are typically familiar with the process of receiving oral therapy, and wish to avoid or defer intravenous chemotherapy. Clinicians value the opportunity to give another line of treatment, with some evidence of response,– particularly intracranially, that may continue to allow patients to function at a high level. Both the registered clinician input and patient input are consistent in their desire to have available this option of therapy.

1.3 Conclusions

In conclusion, there may be a net clinical benefit for lorlatinib in the treatment of patients who progressed on previous alectinib or ceritinib or crizotinib and at least one other ALK inhibitor. This conclusion has some uncertainty, as it is based on a single trial, single arm, phase II trial, with an unplanned pre-specified statistical analysis (i.e. pooled analysis plan for EXP 3B-5 not outlined a priori in the protocol, and the sample size of EXP 3B, EXP 4 and EXP 5 not being powered to detect statistical significance for the primary and secondary endpoints), using surrogate primary endpoints of response rate (40%) and intracranial response rate (50%). The trial lacked a pre-specified determination of what would be considered a clinically significant response rate, and there is a lack of robust data to conclude that a 40% response rate will result in a clinically meaningful benefit with traditional markers of patient benefit such as length or quality of life.

In comparison to best supportive care, it is concluded that lorlatinib does provide and is highly likely to provide an advantage and clinically meaningful benefit in patients with ALK positive cancer, despite the limitations of response rate as an endpoint. This conclusion is based on the historic record of targeted therapy response rates translating to real patient benefit, and the difficulty of treating intracranial disease. It is not clear if lorlatinib is superior to doublet chemotherapy based on a single, phase II trial however, although based on the MAIC it is concluded that lorlatinib has a very high likelihood of being superior to single agent docetaxel or pemetrexed in platinum pretreated patients.

The drug appears to be safe based on this study, and fairly well tolerated. It is impossible to conclude with certainty whether this drug should be sequenced prior to or following doublet chemotherapy (without a randomized phase III trial). However, even without this, it is reasonable to conclude that the drug provides some benefit in comparison to either single agent chemotherapy, or best supportive care, in these patients, as it is a treatment option that may benefit some patients.

Given the relatively low incidence of this cancer, and the preference for oral therapy, this type of phase III trial may be difficult to conduct. Certainly, placebo-controlled trials will not be done, and it appears sequencing studies with doublet chemotherapy will not be performed either. It is also unclear what the threshold for surrogate endpoints such as response rate or PFS should be in order to determine a treatment is more effective than another treatment, or to conclude that it is more beneficial than harmful.

With targeted therapy of a known oncogenic mutation in lung cancer, response rates historically have correlated well with patient benefits, when studied in subsequent randomized trials. However, this has not been formally tested to determine true surrogacy. Indeed, in other pCODR submissions (dabrafenib/trametinib), pERC pointed out that response rate is not a proven surrogate, and the medications were not approved. The CGP believes that this situation is somewhat different with ALK positive disease, as it is clear that these patients have historically benefited from targeted agents in comparison to chemotherapy. In addition, ALK positive disease has a high level of CNS disease and progression, and control is likely to be significantly better with lorlatinib than chemotherapy – the same situation does not exist with BRAF positive disease. It is acknowledged however that while clinicians and patients would value the addition of these options as a treatment, it is extremely difficult to quantify the benefit without a randomized prospective trial.

In response to the PAG questions regarding:

- The eligible patient population for lorlatinib as the pivotal trial had several cohorts but these patients were not included in the reimbursement request (e.g., ALK-positive, treatment-naive patients; ROS1 positive with any previous treatment; and ALK-positive patients with disease progression following previous crizotinib only).
    - Based on the funding requested, patient that are treatment-naive, ROS1 positive with any previous treatment would not be eligible to receive lorlatinib; and ALK-positive patients with disease progression following previous crizotinib only would not be eligible to receive lorlatinib (unless alectinib and ceritinib were not available).
- Guidance on the use of lorlatinib for patients who had prior brigatinib.
    - CGP noted pERC recent recommendation not to reimburse brigatinib.
- Clarity on treatment "as long as the patient is deriving clinical benefit from therapy", treatment duration and treatment discontinuation. In Trial 1001, Patients were allowed to continue treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion.
    - According to the sponsor, clinical benefit was defined as the primary tumor and potential metastases under the treatment of lorlatinib being under better control as opposed to the treatment being completely discontinued. According to the CGP, clinical benefit from therapy = control of most disease, and symptoms, in the absence of significant toxicity, and with any small areas of disease progression dealt with local therapies such as radiation. In general, patients will be continued until significant symptomatic progression, health deterioration, or the availability of a new therapy. With increased local therapies being used for oligometastatic disease, RECIST1.1 criteria for progression become further and further from clinical practice.

- Guidance on sequencing of all oral targeted therapies (i.e., choice of first-line ALK inhibitors as well as other ALK targeted therapies), intravenous chemotherapies and immunotherapies for ALK positive NSCLC.

    - It is the CGP's opinion that in the absence of predictive biomarkers, patients in general will start on alectinib (where available), and switch to lorlatinib at disease progression. Some patients will have been on crizotinib and then alectinib (or crizotinib then ceritinib then alectinib), and then lorlatinib. In several of these patients, they would have already received doublet chemotherapy in the adjuvant or curative setting, or in between treatments while waiting for approval.

    - Following lorlatinib, patients would be given chemotherapy (usually doublet), followed by immunotherapy. The caveat here is that there are other studies in this space using chemo/IO combinations (including chemotherapy/bevacizumab/atezolizumab) that may alter the post lorlatinib or pre-lorlatinib landscape.

- Guidance on the number of ALK inhibitors a patient should receive in their treatment trajectory for ALK-positive NSCLC.

    - In the CGP's opinion, many clinicians would say there is no upper limit, as long as the patient is having benefit. For many of these patients, they may be switched to lorlatinib if available, but if not available, patients may just continue on alectinib post progression. There are other malignancies where it's not uncommon to try each "targeted therapy" (i.e. breast cancer, where patients may receive 5 hormones, and then at times recycle back to one already tried), and if available clinicians would likely adopt a similar approach.

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

In Canada, 1 out of every 2 people are expected to develop cancer in their lifetime. Furthermore, 1 out of 4 Canadians are expected to die of cancer. Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. [17] Non-small cell lung cancers (NSCLC) are the most common type of lung cancers, comprising 85% of lung cancers. [18] In 2019, it is estimated that there will be 29,300 new cases of lung cancer diagnosed and 21,000 deaths associated with lung cancer, with incidence and mortality rates of 51.9/100,000 and 40.2/100,000 respectively. [17] NSCLC represents approximately 85 % of all cases of lung cancer and for the purposes of therapeutic decision, are categorized by histologic appearance as either squamous or non-squamous NSCLC. The majority of patients with NSCLC will present with or develop advanced/metastatic disease. For these patients, treatment intent is to palliate symptoms and prolong survival. In patients with non-squamous NSCLC, the first step in determining treatment options is assessment of molecular markers, including chromosomal rearrangement of the Anaplastic Lymphoma Kinase (ALK) gene on chromosome 2 (ALK positive NSCLC).

ALK fusion positive non-small cell lung cancer is a lung cancer for which no modifiable risk factors are known. It is not caused by cigarette or tobacco exposure, and patients tend to be younger with less tobacco exposure than lung cancer without EGFR mutations or ALK fusions. For advanced lung cancer, the incidence of ALK positive cancers varies, but is thought to be between approximately 2% - 5% of adenocarcinomas. In lifetime non-smokers, the percentage of lung cancers that are ALK positive is approximately 10%, while for former smokers and current smokers the percentage of lung cancers that are ALK positive is lower, likely as a result of an increasing number of non-ALK positive lung cancers in smokers and former smokers. At the population level, regardless of smoking status, the incidence and mortality of ALK positive NSCLC is estimated to be approximately 2-3 per 100 000 per year for incidence and 2 per 100 000 per year for mortality. In Canada, this is expected to be a burden of approximately 700-800 new cases per year, and 600 deaths per year from ALK positive NSCLC.

In these cases, the product of the fusion ALK gene acts as an oncogenic driver, and interrupting ALK signalling with small molecule inhibitors has been a somewhat effective therapeutic strategy in prolonging survival and quality of live with metastatic disease, but does not result in cure. [19] Central nervous system (CNS) metastases are quite common in ALK positive lung cancers, presenting in up to 30 % of patients at diagnosis, and developing in more than 50 % of patients initially treated with crizotinib at some point in their disease course. [20]

2.2 Accepted Clinical Practice

Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, was until recently the accepted first-line therapy for metastatic ALK-positive NSCLC in Canada and funded for this indication. This was 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. [21] Crizotinib is continued in the absence of disease progression or unacceptable toxicity, and is often continued past radiologic progression if a patient is not symptomatic, in large part because the alternative has

been cytotoxic chemotherapy. In the PROFILE 1014 trial, 73% of patients were treated beyond progression with crizotinib, for a median of 3.1 months. However, 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. [16] In addition, the Central Nervous system (CNS) is a very common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS, coupled with the high incidence of CNS metastases for this subset of lung cancer.

The second generation ALK inhibitor, ceritinib has demonstrated ability to overcome resistance to crizotinib and is shown to provide durable responses and meaningful benefit in terms of progression free survival in both crizotinib resistant and crizotinib naive patients. [22] In the randomized phase III trial ASCEND-5, ceritinib was superior to single agent pemetrexed or docetaxel in ALK positive patients who had been previously treated with crizotinib and platinum doublet chemotherapy. [15] Once was only available through a special access program, now ceritinib it is currently publicly funded in Canadian provinces. [23]

For patients with ALK positive advanced NSCLC progressing on crizotinib – either CNS or non-CNS - alectinib or brigatinib are newer ALK targeted agents that can be used, having activity in crizotinib resistant CNS and non-CNS disease. Funding for second line alectinib was recently approved in most jurisdictions in Canada, based on the ALUR study, [14] and it is anticipated that the majority of patients who receive first line crizotinib and progress will subsequently be treated with alectinib monotherapy. The median progression free survival time with second line alectinib was approximately 10 months, in comparison to less than two months with standard chemotherapy. It is anticipated that for the next two years, the majority of patients progressing on alectinib will be those who received crizotinib followed by second line alectinib.

Alectinib was then compared to crizotinib as first line therapy, in the ALEX and J-ALEX trials, [24,25] and underwent a health technology assessment through pCODR in 2018. For patients receiving alectinib as first line treatment, the median time until progression or death was shown to be almost three years. [26] This superiority of alectinib or crizotinib led to the recommendation that alectinib be considered for first line funding in the ALK positive population, pending cost-effectiveness being improved to a reasonable level. If alectinib becomes widely available for first line therapy, it is anticipated that the vast majority of patients with known ALK positive advanced disease over the next several years will be receiving alectinib monotherapy as first line treatment.

Treatment Post Alectinib

Although effective in many patients, there is still a clinical progression rate in the CNS and non-CNS for patients receiving alectinib, or similar non-crizotinib ALK inhibitors (i.e. brigatinib) that requires alternate therapy. For isolated metastatic growth in CNS or non-CNS - "oligoprogression" – consensus is to continue the alectinib for continued control of the majority of disease, and treat the growing lesion or lesions with local modality therapies such as stereotactic radiotherapy. For patients who progress in multiple areas, real world treatment patterns have not been well reported at the population level. However, algorithms and guidelines recommend using doublet platinum chemotherapy at this time, in an effort to control disease until an additional ALK inhibitor can be attempted. Carboplatin – Pemetrexed with maintenance pemetrexed is the most common regimen thought to be used. Chemotherapy combination therapy with immunotherapy has not been studied in a phase III setting, and is not recommended. Monotherapy with immunotherapy, such as pembrolizumab is not recommended prior to chemotherapy, even in PD-L1 strongly positive patients. After progressing on alectinib

and doublet chemotherapy, docetaxel and PD-L1 pathway inhibitors may each be tried, but responses and benefit are very low. Best supportive care practices – including symptom management with agents such as opioids and steroids, radiation therapy for symptomatic lesions, and palliative and end of life care – are typically practiced at this stage.

Resistance to Alectinib and Lorlatinib

Most patients with ALK positive lung cancer will eventually develop resistance to targeting ALK with alectinib. As with most oncogene driven cancers, there are multiple potential resistance mechanisms: including the increased use of alternate growth pathways being used (i.e. ALK independent mechanisms), or the result of mutations in the ALK protein itself rendering it resistant to inhibition from the current method of ALK inhibition (ALK dependent). In vitro, certain cells that had acquired resistance to alectinib through ALK dependent mechanisms, such as G1202R, remain sensitive to lorlatinib. While this mutation is recognized using research grade assays, there are no clinical grade tests that are used to select for who will and who will not benefit from lorlatinib.

Lorlatinib is yet another oral ALK targeted tyrosine kinase inhibitor, with good CNS penetration, and with some in vitro activity against cancer cells resistant to alectinib. It was then tested in a multi-cohort Phase 2 trial, involving multiple ALK positive settings with clinical relevance - including those settings that form the current submission - ALK-positive NSCLC who have previously received alectinib as first, or crizotinib and a subsequent generation drug with had progressive disease. Based on phase II evidence, lorlatinib has some activity in this patient population in both CNS disease and non-CNS disease settings. Lorlatinib was not tested against the previous standard of care (platinum doublet chemotherapy), although a reasonable assumption would be that the standard of care arm would have similar or worse outcomes for disease control than the control arm of platinum doublet chemotherapy from earlier line trials with the same disease – i.e. the ALUR trial.

2.3 Evidence-Based Considerations for a Funding Population

The Canadian Cancer Society estimates that in 2019, there are approximately 29,300 new cases of lung cancer in Canada. [17] A true determination of this number could likely be inferred from the new prescription rates for crizotinib or alectinib, should that data be available. Determination of ALK positivity in Canada is standard, and uses an immunohistochemistry test to screen advanced non-squamous NSCLC, with confirmation in equivocal cases by fluorescent in-situ hybridization. [27] Testing for ALK rearrangements would have been done previously in the population under consideration for this indication, as they would have received prior crizotinib and alectinib as initial ALK-directed therapy.

Of patients who receive crizotinib, a second generation ALK inhibitor and progress; or patients who receive alectinib and subsequently progress, it is unclear how many of these patients would be eligible to receive lorlatinib. Patients may receive one line of therapy and not a subsequent line, due to catastrophic events (pulmonary embolism, sudden death etc.), decrease in performance status, treatment fatigue, intercurrent illnesses etc. When moving from first line chemotherapy to second line chemotherapy, the number of patients drops substantially. We do not have accurate data for targeted therapy such as the ALK positive population. An estimate would be 60% of patients who progress on alectinib would subsequently receive lorlatinib if available. This number may decrease if a companion diagnostic test were developed that could predict who will continue to benefit from ALK inhibition.
In terms of consideration for funding, there will be several groups of patients with different treatment pathways who need to be considered, who will likely enter the period when they would benefit from lorlatinib at different times. For patients diagnosed with ALK positive NSCLC

prior to 2015, the majority of these patients would have been treated with first line chemotherapy, followed by crizotinib, followed by alectinib or other second generation ALK inhibitor. For patients diagnosed after 2015 (in most provinces), these patients would be treated with first line crizotinib, followed by chemotherapy or second generation ALK inhibitor. For patients newly diagnosed with ALK positive disease currently and in the next few years, they would be expected to receive alectinib monotherapy, and have a median PFS of approximately 3 years. Complicating these different pathways are the various numbers of patients accessing alectinib or other ALK inhibitors on clinical trials, industry sponsored access programs, or through private insurance.

From a funding perspective, CADTH does not have a clear separate process for rare disease, but ALK positive lung cancer should be seen as a rare disease, rather than as a rare subset of a common disease. There are significant practical challenges of conducting a robust phase III clinical trial in the post alectinib space, and there is a significant unmet medical need for these unfortunate patients with a rare tumour.

2.4 Other Patient Populations in Whom the Drug May Be Used

The only population that would be eligible would be those for whom alectinib has failed – including those who received other ALK inhibitors or other anti-cancer agents in addition to alectinib. There are few patients who are intolerable of alectinib, or need to stop it for reasons other than progression, for whom lorlatinib may be considered.

For patients who do not receive alectinib due to financial reasons (i.e. not provincially funded), it is possible they would use lorlatinib if available, but outside of a major price difference it is unlikely that lorlatinib would be funded without alectinib also being funded.

3 SUMMARY OF PATIENT GROUP INPUT

The following patient groups provided input on lorlatinib and their input is summarized below: The Ontario Lung Association (OLA) and Lung Cancer Canada (LCC).

OLA collected information through phone interviews and an online survey:

> -Two phone interviews with patients living with lung cancer (completed in April 2019 and November 2018)
>
> -One phone interview with a caregiver of someone living with lung cancer (March 2019)
>
> -Two phone interviews with patients living with chronic lung conditions (March 2019)
>
> -90 on-line surveys completed by people living with a chronic lung condition and / or their caregivers (input received between December 2018 - April 2019). 3 were completed by people living with a diagnosis of lung cancer and the remainder were patients with a chronic lung condition or their caregivers.

All data gathered was from people residing in Canada. As well, a certified respiratory educator reviewed sections related to disease experience and experience with available treatments. None of the respondents had experience with lorlatinib.

LCC collected information through the following:

> -A national survey, the Faces of Lung Cancer survey was administered online in August 2015. Ninety-one patients responded; all have or have had lung cancer. Seventy-two caregivers responded; all were caring for, or previously cared for patients living with lung cancer.
>
> -An environmental scan of online forums and patient interviews was conducted which included information from fourteen individuals. Interviewed patients were sourced through social media, online requests, word of mouth and known patients. Twelve patients and two caregivers ranging from 31-76 years old provided input for this submission. Six had participated in the environmental scan, while eight had been interviewed. Of the interviewees, 2 were from the U.S. while 6 were in Canada. Location information was not available for participants in the environmental scan. Data from the interviews and environmental scan were collected from May-June 2019. Eleven patients and both caregivers had experience with lorlatinib (respondents would have been eligible based on the reimbursement request). The input included patient and caregiver perspectives on previous and current treatments as well as their needs.

Symptoms patients experience with lung cancer include pain, shortness of breath, cough, weakness and fatigue. These symptoms impact the ability of patients to be independent and functional. Lung cancer can also affect the emotions, relationships and finances of patients and caregivers. Current treatments for NSCLC include chemotherapy and targeted therapy with ALK inhibitors.

From a patient's perspective, outcomes that need to be addressed include: to stop or slow the progression of disease, reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy. Patients value having treatment options that control disease, delay progression, prolong survival and manage side effects; and quality of life. Patients would like more treatment options and would be willing to try additional or combination treatments if the side effects were no worse than their current treatment.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. 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 NSCLC

A diagnosis of lung cancer is devastating to patients. Many patients were shocked by their diagnosis, especially those who were young, non-smokers, or otherwise healthy. One patient diagnosed with stage 4 ALK+ lung cancer shared with LCC, "I've never been a smoker, so I never dreamed I could have lung cancer. I was completely shocked! It felt like my world had turned upside down". Patients were concerned about available treatment options, survival, and their loved ones.

Patients also shared frustration about the number of appointments and length of time it took to receive an accurate diagnosis. One patient told the OLA, "It took close to a year, with many appointments and referrals to finally get to the right specialist and receive a proper diagnosis and learn about my prognosis." This caused added stress and anxiety for patients and their families. The daughter of a lung cancer patient explained, "The most frustrating thing for me was how long it took to get her diagnosed."

Symptoms of lung cancer include: pain (very intense at times), shortness of breath, cough, weakness, and extreme fatigue/exhaustion. These symptoms change frequently, which can be difficult to manage. According to the OLA, several patients also experienced chest tightness, chest pain, sleep disturbances, and increased airborne/allergy triggers. Lung cancer impacts many aspects of day-to-day life for patients. One patient said "It takes longer to get dressed and do my personal hygiene. My ability to carry out daily tasks and activities is greatly reduced, and I can no longer lift heavy objects. I can't walk distances and get tired very quickly." It affects the ability to work, travel, socialize and participate in leisure and physical activities. Patients often had to plan their day around managing their exhaustion: "If I go out in the morning, that's it for the day. I do not have the energy to do anything else." It also affects relationships with family and friends, independence, emotional wellbeing and their financial situation. The isolation and loss of independence often led to depression for patients.

After diagnosis, OLA interviewees found that they had little information about the disease (either cancer or lung cancer specifically), its treatment options, and the prognosis in terms that would apply to them. They needed information in plain language to help them understand their situation and make decisions about next steps. They found it difficult to find someone to take the time to speak with them and felt that their appointments were rushed, "…I never feel that I am given enough time to ask (and understand) everything I want to." Several patients mentioned they would like to receive information in "easy to understand" language and a clear picture of their treatment choices.

3.1.2 Patients' Experiences with Current Therapy for NSCLC

Patients interviewed by the OLA had tried the following treatments: Spiriva, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza and Ventolin (as needed). One patient was on "too many medications to list", one patient was undergoing radiation, and one patient was the recipient of a double lung transplant in 2018.

Respondents reported that some treatments provided some relief for symptoms including fatigue, shortness of breath, cough, appetite loss and low energy; however, there were side effects like palpitations, dry mouth, and mouth sores, "light-headedness", "dizziness", shakiness, impact on mood, loose bowels, headaches and difficulty sleeping. None of the interviewees entertained the idea of not being treated, even those with

advanced disease. Some mentioned dose reduction as an option to try and better manage the side effects of the medications.

According to LCC, the current standard of care for ALK+ lung cancer patients typically involves crizotinib used in the first line and post intolerance or progression. A second-generation inhibitor such as alectinib, brigatinib, or ceritinib is used thereafter. If approved, lorlatinib would follow these next generation inhibitors. If alectinib was used as first line treatment instead of crizotinib, lorlatinib would be a second line option. In both scenarios, lorlatinib is placed ahead of chemotherapy and immunotherapy. For ALK+ NSCLC patients who have progressed on or who were intolerant on crizotinib, current treatment is chemotherapy, ceritinib or alectinib.

Chemotherapy has long been used as standard treatment for lung cancer side effects include nausea, vomiting and extreme fatigue. Some patients experience minimal symptoms, while others experienced interference with daily activities. Chemotherapy is also known to lower patients' immunity, resulting in an inability to go out or receive visitors. This lowered immunity, along with the other side effects, affected patients' ability to work, resulting in financial hardship. Patients were inconvenienced by the need for multiple hospital visits for intravenous infusions as well as the toxicities and after effects associated with the treatment. A few patients surveyed by LCC had their cancer controlled by chemotherapy, though it eventually progressed.

In contrast, patients reported mostly positive experiences with targeted therapy, specifically with alectinib and ceritinib. Both treatments had manageable side effects, including gastrointestinal (GI) symptoms. Ceritinib has GI side effects, documented in previous pCODR submissions. Targeted therapy has led to improved outcomes such as tumour shrinkage, brain metastasis and prolonged survival. Six weeks of treatment with alectinib reduced one LCC patient's tumour by 70%, with few side effects. One patient was on ceritinib for two years and showed no evidence of disease for about a year. Another patient developed brain metastasis while on crizotinib and ceritinib helped with the metastasis. One patient was on ceritinib for 18 months before unfortunately progressing.

Targeted therapy has changed both the outcomes and quality of life for ALK+ patients, who were functional, independent, and active. A patient treated with alectinib said, "It allowed me to live." The LLC input describes patients who have been able to live and thrive because of targeted therapy, including lung cancer survivors. Patients were able to return to work or care for their families. The side effects did not interfere with daily activities and the oral treatment did not require hospital visits or recuperation time.

3.1.3 Impact of NSCLC and Current Therapy on Caregivers

With a survival rate of 17%, caregivers worried that a diagnosis of lung cancer was a death sentence. The Faces of Lung Cancer survey revealed that the burden of a diagnosis of lung cancer while felt by the patient, in some cases caregivers seemed to carry the burden more a than the patients themselves. Caregivers experienced anxiety, worry, depression and even psychological distress which impacts their quality of life and the patient as well.

When patients were treated with chemotherapy, caregivers were faced with the provision of care, the need to help take their loved ones to their appointments, as well as having to juggle other needs at home and at work. This sometimes results in many caregivers losing time at work and subsequent reduced productivity. One caregiver quoted the following to the OLA. "Before my husband passed away from his lung cancer, all I did was care for him. It was an all-consuming job." The Faces of Lung Cancer survey showed that over half of the caregivers (59%) reduced the number of hours they worked, and a further 8% quit their jobs.

With an oral form of dosage and less and more manageable side effects, patients were independent, functional and active. This allowed caregivers to continue working and be productive.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences to Date with Lorlatinib

Eleven patients and two caregivers shared their experiences with lorlatinib with LCC. Their experiences are summarized in table 3.1.

Table 3.1 Patient experiences with lorlatinib (Lung Cancer Canada)

Gender	Age	Caregiver/ Patient	Period on Lorlatinib	Status
Male	N/A	Caregiver	3 years	Stable
Male	60	Patient	3 years	Has had oligo progression in lymph nodes which was treated with targeted radiation still continues on lorlatinib
Male	32	Patient	3 years	In remission
Female	N/A	Patient	N/A	N/A
Female	39	Caregiver	6 months	Improved symptoms
Female	59	Patient	5 years	Progression
Female	40	Patient	3 years	NED
Female	53	Patient	10 months	Stable
Male	31	Patient	13 months	Stable
Female	49	Patient	6 months	Awaiting scan results but feels better
Male	76	Patient	1 month	Improved symptoms
Male	56	Patient	12 months	Was stable, but current scans show liver infiltration
Male	69	Patient	6 months	Stable
Female	50	Patient	6 months	Stable

Many patients said that side effects of lorlatinib were manageable. Furthermore, one patient found lorlatinib to be the easiest of the three ALK inhibitors they had taken. Another patient said that the side effects were much better compared to chemotherapy and crizotinib. Patients credited lorlatinib for improved symptoms, stable disease, and increased ability to function. Some patients were able to return to work or resume regular physical activity. Patients were also able to spend more time with friends and family.

Progression while on crizotinib and ceritinib, especially brain metastasis, was a concern for patients. Many patients said they switched to lorlatinib because of this concern. One patient who developed brain metastases on crizotinib and progressed after radiation and ceritinib followed by alectinib showed improvement after 13 months on lorlatinib.

The side effects experienced by patients are summarized in Table 3.2. For two of the patients, responses were provided by their caregivers. Some patients required treatment to manage side effects, including counselling, anti-depressants and medication to manage depression and high cholesterol, respectively. One caregiver described how cognitive impairment from radiation increased for the patient while on lorlatinib: “The increase is reversed when she is taken off the drug so it is a trade off for her keeping her cancer stable with the drug or less cognitive impairment when off the drug.”

Table 3.2 Side effects experienced by patients while on lorlatinib (Lung Cancer Canada)

Side Effect	Number of Patients, n (%)
Neuropathy	7 (50%)
Cognitive and memory issues	7 (50%)
Increased cholesterol	6 (43%)
Edema	5 (36%)
Weight gain	5 (36%)
Mood changes	2 (14%)
Dizziness	2 (14%)
Total responses	14

Despite experiencing side effects, patients interviewed by LCC were able to maintain functionality and a good quality of life. They were able to continue working, spend time with loved ones, and be physically active. They generally felt more energized and hopeful about their futures. In the words of one patient, "Lorlatinib saved my life."

Patients interviewed by the OLA expected to have greater treatment options to choose from and most would be willing to try additional and/or combination treatments if the adverse effects were no worse than those from the current treatment. Patients would like to do treatment at home, removing the need for the patient or caregiver to take time off work.

Outcomes that patients and their caregivers would most like addressed are the following: to stop or slow the progression of disease, reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy. Patients emphasized a desire for more energy, to be able to do more each day before the exhaustion sets in. They value quality of life and want to experience improved independence and require less assistance from others. Patients and caregivers would like the following current side effects reduced or eliminated: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. They would also like there to be less or no cost burden associated with new treatments.

3.3 Additional Information

With ALK inhibitors becoming the standard of care, a need for more options was expressed. According to LCC, ALK+ patients want more treatment options that maintain a good quality of life. With first line alectinib in pricing negotiations, it may replace crizotinib as a preferred first line option. In that case, patients would benefit from more second line options. Furthermore, lorlatinib can also introduce marketplace competition.

LCC noted that patients post crizotinib or other ALK inhibitors would have already been tested for the ALK biomarker before treatment. As a result, companion diagnostic tests would not be required for lorlatinib and would not pose a burden on the healthcare system.

LCC also expressed that approval of lorlatinib on the basis on phase II data would enable collection of third line data while allowing patients to continue living their "new normal".

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 (www.cadth.ca/pcodr). 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) and a federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Eligible patient population
- Comparative data to brigatinib, ceritinib as well as alectinib

Economic factors:

- Pricing structure of lorlatinib

Please see below for more details.

4.1 Currently Funded Treatments

Currently, second-line and beyond treatment options for patients with ALK-positive NSCLC who have failed crizotinib and at least one other ALK inhibitor, or who have progressed on ceritinib or alectinib, include chemotherapy (docetaxel, platinum doublet or pemetrexed), erlotinib, and immunotherapy (atezolizumab, nivolumab or pembrolizumab). At the time of the PAG input, ceritinib is funded in most jurisdictions, alectinib has been recently reviewed at pCODR, and brigatinib is currently under review at pCODR.

PAG is seeking information on whether comparison data is available comparing lorlatinib to brigatinib, ceritinib, as well as alectinib.

4.2 Eligible Patient Population

Although NSCLC is a common cancer, lorlatinib would only be indicated for patients with ALK positive NSCLC and who have failed crizotinib and at least one other ALK inhibitor, or who have progressed on ceritinib or alectinib, which would be a small number of patients.

PAG is seeking clarity on the eligible patient population for lorlatinib as the pivotal trial had several cohorts but these patients were not included in the reimbursement request (e.g., ALK-positive, treatment-naive patients; ROS1 positive with any previous treatment; and ALK-positive patients with disease progression following previous crizotinib only).

Brigatinib is currently under review at pCODR for ALK-positive, locally advanced or metastatic NSCLC. PAG is seeking guidance on the use of lorlatinib for patients who had prior brigatinib.

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

- Patients who are currently receiving other second-line or beyond treatments (e.g., third ALK inhibitors of ceritinib or alectinib, immunotherapy or chemotherapy who have had prior crizotinib) and have not progressed.

4.3 Implementation Factors

Lorlatinib is an oral tablet with two strengths, dose adjustment is accomplished by adjusting the number of tablets to take. This is an enabler to implementation. At the time of the PAG input, the price of lorlatinib was not available. PAG is seeking information on the cost and noted that flat pricing of all tablet strengths is more costly for patients who are dispensed the lower strengths and adjusting dose by adjusting the number of tablets.

PAG is seeking clarity on treatment "as long as the patient is deriving clinical benefit from therapy", treatment duration and treatment discontinuation.

As lorlatinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation. However, there would be increased pharmacy resources (preparation and dispensing of lorlatinib) and clinic visits for monitoring of associated side effects.

PAG noted that lorlatinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration as an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on sequencing of all oral targeted therapies (i.e., choice of first-line ALK inhibitors as well as other ALK targeted therapies), intravenous chemotherapies and immunotherapies for ALK positive NSCLC.

PAG noted clinicians may prefer to use available ALK inhibitors sequentially rather than alternatively. Lorlatinib is the fifth ALK inhibitor available for ALK-positive NSCLC, PAG is seeking guidance on the number of ALK inhibitors a patient should receive in their treatment trajectory for ALK-positive NSCLC.

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two joint registered clinician input submissions were provided, representing a total of nine clinicians. One joint submission on behalf of seven clinicians (one oncologist, 6 unspecified) were from Lung Cancer Canada (LCC) as well as one joint submission on behalf of two clinicians from Cancer Care Ontario Lung Drug Advisory Committee were received for the review of lorlatinib as monotherapy for ALK-positive metastatic NSCLC who have progressed on crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

Clinicians consider access to multiple lines of ALK directed therapy to be valuable for ALK-positive patients as there is an unmet need for these patients. Access to new therapies translates directly into improved overall survival outcomes. The primary benefit of lorlatinib is that it acts as an additional line of therapy before chemotherapy for this indication. It does not replace any current treatments. Compared to lorlatinib, other treatment options (chemotherapy, immunotherapy) offer limited benefit and greater toxicity. Clinicians find the eligibility criteria for the phase II trial applicable to clinical practice. In treatment sequence, lorlatinib should follow use of a next generation ALK inhibitor. Clinicians did not find conclusive evidence to support the number of ALK inhibitors a patient should receive in their treatment trajectory. Companion testing is not required for lorlatinib.

LCC added an additional consideration: Past pCODR submissions and clinical experience have demonstrated remarkable consistency between phase II and phase III targeted therapy clinical trial results. Therefore, they suggest that the positive results in the phase II trial prove lorlatinib's potential. They caution that a delayed positive recommendation means unnecessary delays in patient access.

Please see below details received from the registered clinicians.

5.1 Current Treatment(s) for Non-Small Cell Lung Cancer

The first line standard of care is targeted therapy with an ALK inhibitor. Historically, the standard therapy was crizotinib, a first generation ALK inhibitor. Crizotinib demonstrated superiority over chemotherapy in the PROFILE 1014 clinical trial. On progression, the standard is continuation of ALK targeted therapy with next generation ALK inhibitors (most commonly alectinib, sometimes brigatinib and rarely ceritinib). In the updated overall survival (OS) analysis for PROFILE 1014, patients who had access to crizotinib followed by a next generation ALK inhibitor had significantly improved survival compared to patients who only had access to crizotinib. Similar findings were seen in the French nationwide cohort retrospective study (CLINALK).

LCC states that currently, next generation ALK inhibitors are becoming the standard of care for first line ALK rearranged NSCLC. This is based on the ALEX study, which demonstrated an improvement for alectinib over crizotinib and led to a positive pCODR recommendation for first line alectinib. There is also recently presented data showing similar benefits for brigatinib over crizotinib in the first line ALTA 1L study.

LCC also notes that in both "historical patients" who started their journey with first line crizotinib followed by a next generation ALK inhibitor, as well as "newer patients" who are starting their treatment with a next generation ALK inhibitor (typically alectinib), the main available options on progression include chemotherapy and immune therapy. The randomized phase III ALUR study which investigated alectinib versus chemotherapy demonstrated a marked benefit for the targeted therapy approach versus standard chemotherapy. LCC highlights the importance of continuing to treat oncogene driven cancers with effective targeted therapies

before switching to other alternatives. Clinicians from CCO identified chemotherapy as the current standard of care, though some patients may receive radiation.

5.2 Eligible Patient Population

Clinicians identified a critical unmet need for patients with ALK rearranged NSCLC, for both "historical patients" who have progressed on first line crizotinib and a second line next generation ALK inhibitor as well as "newer patients" who have progressed on a first line next generation ALK inhibitor. For both groups of patients, lorlatinib would be used after progression on a next generation ALK inhibitor.

Clinicians identified that the inclusion and exclusion criteria from the study are applicable to clinical practice. Both historical and newer patients were included in separate cohorts in the clinical trial. Patients with brain metastases are a subgroup of interest to clinicians at LCC. Brain metastases are a common area of progression in ALK rearranged NSCLC and is a specific area where effective treatments are needed, given both the significant short and long-term effects of brain radiation in these patients.

There is no additional testing required to identify patients for lorlatinib. While there is interest in trying to identify molecular subgroups, who may benefit differentially from lorlatinib, this is not yet ready for clinical practice. This relates to the retrospective and very limited nature of the available data. Also, testing for ALK resistance mutations is not currently available in clinical practice in Canada.

5.3 Relevance to Clinical Practice

The clinicians from LCC indicated they had experience using lorlatinib, while clinicians from CCO did not.

Studies have shown a marked benefit for targeted therapy over chemotherapy, as well as less toxicity, which translates into improved quality of life. This evidence comes from numerous randomized phase III trials in the first and second line setting, including the ALUR study. Chemotherapy has limited effectiveness for brain metastases, a common and devastating problem for these patients. Therefore, chemotherapy is generally reserved for when ALK directed therapy has been exhausted (i.e. post progression on lorlatinib). The data from the phase II study show higher systemic and intracranial responses with lorlatinib compared to historical results of other potential options (especially chemotherapy and immune therapy).

Targeted therapy drugs, including lorlatinib, have shown marked and durable responses, CNS responses and excellent tolerability compared to historical data for chemotherapy. Clinicians find phase II data to be readily acceptable to adopt new treatments in the case of target therapy. It would be ethically and practically difficult to design a randomized study of lorlatinib versus chemotherapy, and the limitations of chemotherapy versus a targeted therapy are well described in the literature.

As with chemotherapy, there is no equipoise to compare lorlatinib to immunotherapy in a phase III study. Large academic registries (like IMMUNOTARGET) as well as other series have demonstrated lower clinical benefits of immunotherapy in ALK cancers compared to non-oncogene driven NSCLC. Like chemotherapy, the CNS activity of immunotherapy is limited compared to lorlatinib. Clinical use of immunotherapy is reserved as a last line of therapy.

Once a patient has progressed on a next generation ALK inhibitor, there is limited data to support the use of "one of the other available ALK inhibitors" as the next line of therapy. As next generation ALK inhibitors are increasingly used in the first line setting, crizotinib use in ALK

rearranged patients will be near obsolete. Ceritinib is not a commonly used ALK inhibitor due to significant GI toxicities and relatively lower clinical benefits seen in cross trial comparison with other ALK inhibitors. Brigatinib is currently being evaluated both in the first line and in the "post alectinib" setting.

In conclusion, once a patient has progressed on a next generation ALK inhibitor, the available data for lorlatinib efficacy, combined with CNS efficacy and a favourable toxicity profile make lorlatinib the default next option for these patients versus chemotherapy, immune therapy, or another available ALK inhibitor.

Lorlatinib has a few unique side effects for clinicians to treat. Elevated lipids, especially triglycerides may require medical management. Also, due to the CNS penetration of the drug, there are neurocognitive effects that may require dose modification.

Clinicians suggest that treatment with a new ALK inhibitor like lorlatinib, that can overcome resistance to a next generation ALK inhibitor, will lead to further improvements in survival for patients. LCC notes that this type of data will take several years to mature, especially given that lorlatinib was just recently approved in the US and Europe.

5.4 Sequencing and Priority of Treatments with Lorlatinib

Clinicians would not replace any treatment with lorlatinib but would use it after progression on a second generation ALK inhibitor. Clinicians from LCC indicated two sequence options for the use of lorlatinib:

Scenario 1
1) Crizotinib
2) Next generation ALK inhibitor (either one of alectinib, brigatinib, ceritinib)
3) Lorlatinib
4) Chemotherapy
5) Clinical trial or immunotherapy

Scenario 2
1) Next generation ALK inhibitor (typically alectinib, potentially brigatinib)
2) Lorlatinib
3) Chemotherapy
4) Clinical trial or immunotherapy

In both scenarios, lorlatinib becomes a new option for patients who progress on a next generation ALK inhibitor. One clinician noted that alectinib is the best first line and for patients who progress, lorlatinib would be a good second line option. It is unclear how brigatinib and ceritinib will fit in, however lorlatinib is a preferred second line option. CCO notes that most clinicians do not use crizotinib as first line treatment.

According to LCC, lorlatinib acts as an additional line of therapy before chemotherapy. Clinicians from LCC expect that future data and national development of tumour/blood based ALK resistance mutation testing may further guide the sequencing of treatments, including potential use of an additional next generation ALK inhibitor before or after lorlatinib.

Each ALK inhibitor has a unique side effect profile. Overall, lorlatinib is well tolerated with some unique side effects as outlined above. It has a highly convenient dosing schedule for patients compared to other agents, where patients can take a single pill once daily.

5.5 Companion Diagnostic Testing

There is no companion diagnostic testing required for lorlatinib. ALK testing is widely available at diagnosis of NSCLC, typically through immunohistochemistry (and/or FISH, NGS), and is funded.

ALK resistance testing through NGS at progression on a next generation ALK inhibitor is not currently supported by available data or clinical guidelines and is not easily accessible in the Canadian landscape.

5.6 Implementation Questions

5.6.1 Is there evidence to support the number of ALK inhibitors a patient should receive in their treatment trajectory for ALK-positive NSCLC?

LCC did not find clear data to support the number of ALK inhibitors a patient should receive. While there are a multitude of ALK inhibitors available and there are some patients who can respond to more than one next generation ALK inhibitor (e.g., alectinib, then ceritinib, then brigatinib), these cases would be less frequent and there is a lack of data to guide that approach. As such, lorlatinib would generally be the treatment of choice post progression on a second generation ALK inhibitor.

Similarly, the CCO DAC has currently found no good evidence for this implementation question. Lorlatinib is the only ALK inhibitor with evidence that adding an ALK inhibitor in a pre-treated population is beneficial.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and effect of lorlatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on: crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized and non-randomized controlled trials, Single arm trials (in the absence of comparative evidence)	Adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on second generation ALK inhibitors	Lorlatinib monotherapy	Chemotherapy Best supportive care	-Overall Survival - Progression Free Survival - Overall response rate -Duration of Response -Safety -Quality of Life -Time to progression -intracranial pressure
RCT: Randomized Control Trial; ALK: anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer				

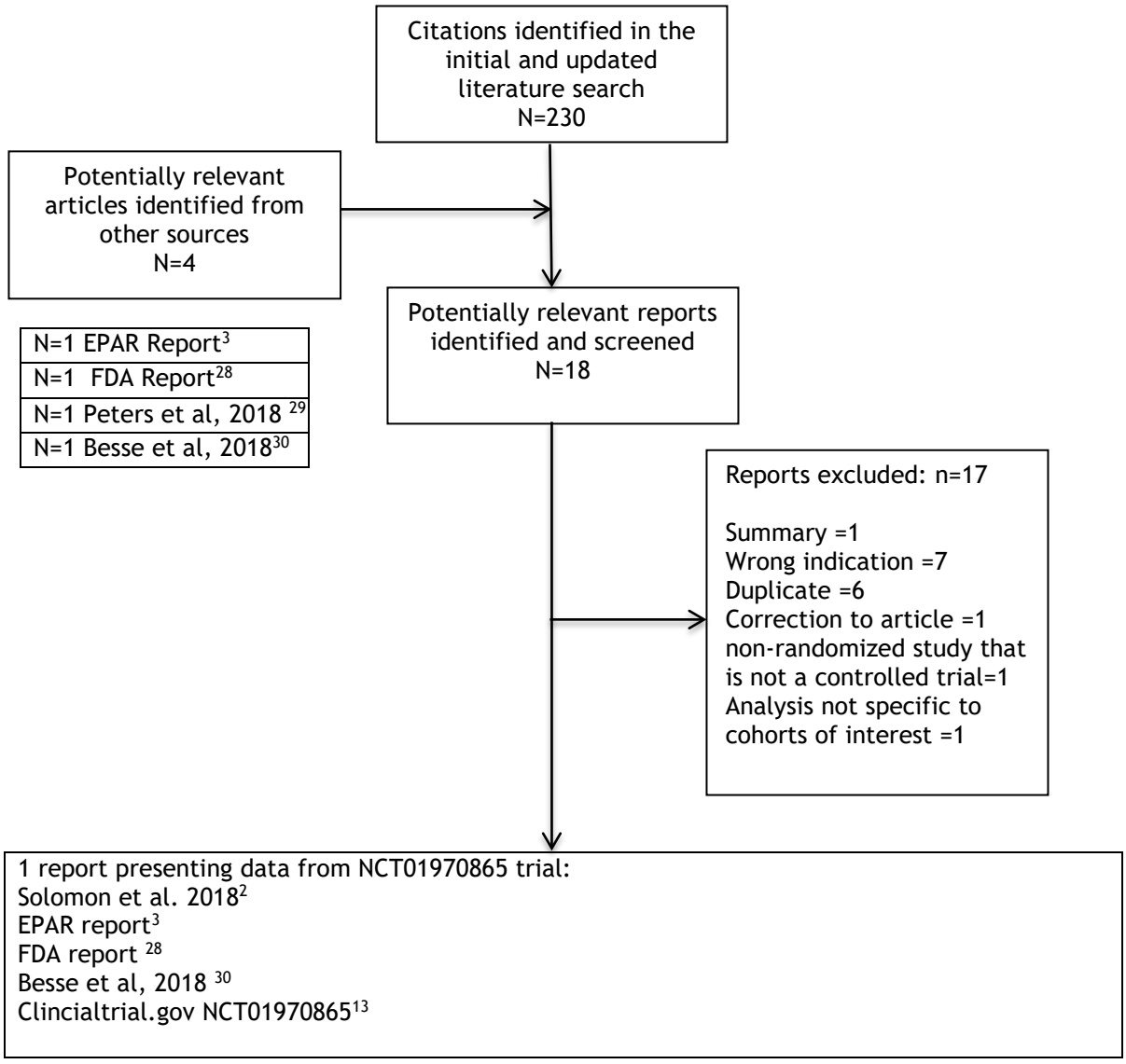
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Among the 18 potentially relevant reports identified by the search, 1 study[2] , 1 European Public Assessment Report and 1 FDA report were included in the pCODR systematic review and 17 studies were excluded.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to checkpoint meeting response,[7] clinical summary[4] and clinical study report[6] were also obtained through requests to the sponsor by CADTH.

6.3.2 Summary of Included Studies

One phase II study (Trial 1001) was included in this systematic review. The key characteristics of this study are summarized in table 4. Although this phase II trial is comprised of several cohorts, only EXP 3B-5 is of interest for this review.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Phase II study (Trial 1001)

Trial Design	NCT01970865 Phase II ongoing, multicentre, open-label, single-arm study N=276(Enrolment between September 15, 2015 and October 3, 2016) across 47 centres in 14 countries, including Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Singapore, Spain, Switzerland, Taiwan, and United States (US). Ultimately, Belgium did not enroll any patients. [3] Funded by Pfizer. Data are presented for the following data cut-offs: March 15, 2017 and February 2, 2018 The sponsor stated a new efficacy results update is planned to be available in Q2 2020.[7]
Inclusion Criteria[5]	• Adults (≥18 years) with histologically or cytological confirmed diagnosis of metastatic NSCLC that carried either an ALK rearrangement or ROS1 rearrangement Disease Status Requirements: • Disease progression after 1 prior ALK inhibitor therapy other than crizotinib. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP 3B]; • Disease progression after 2 prior ALK inhibitor therapies. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP 4]; • Disease progression after 3 prior ALK inhibitor therapies. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP 5] • All patients had at least 1 measurable target extracranial lesion according to RECIST version 1.1. • ECOG: 0-2 • Adequate bone marrow, pancreatic, renal and liver function • Acute effects of any prior therapy • Serum pregnancy test (for females of childbearing potential) negative at Screening

	• Informed consent and willingness to comply with study procedures • Male and female patients of childbearing potential and at risk for pregnancy were required to agree to use 2 highly effective methods of contraception
Exclusion Criteria[5]	• Spinal cord compression • Major surgery within 4 weeks of study entry • Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) completed at least 48 hours prior to study entry • Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study entry • Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways • Previous high-dose chemotherapy requiring stem cell rescue and prior irradiation to >25% of the bone marrow. • Bacterial, fungal, or viral infection including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. • Severe acute or chronic medical or psychiatric condition, cardiovascular disease and acute pancreatitis, active malignancy within last 3 years, active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease or previous gastric resection or lap band. • Current or anticipated use of strong or moderate CYP3A4 inhibitors (administration within 10 days), strong CYP3A4 inducers (administration within 12 days), CYP3A4 substrates (administration within 12 days), CYP2C9 substrates, CYP2B6 substrates, strong CYP2C19 inhibitors (administration within 12 days), strong CYP2C8 inhibitors (administration within 12 days) • Patients with abnormal left ventricular ejection fraction • Female patients breastfeeding
Intervention[2]	Lorlatinib was administered in a tablet form beginning with a dose of 100 mg given once daily continuously in 21-day cycles. Treatment was expected to continue until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients were permitted to resume treatment with lorlatinib after objective progression provided there was clinical benefit based on the investigator's opinion.
Comparator	Not applicable. Single arm trial

Trial Outcomes	Primary Outcome -ORR -Intracranial ORR Secondary Outcomes -Duration of Response -Intracranial duration of response -Time to first tumour response -Time to tumour progression -PFS -OS -Safety -Patient-reported Outcomes

Table 5: Select quality characteristics of included studies of lorlatinib

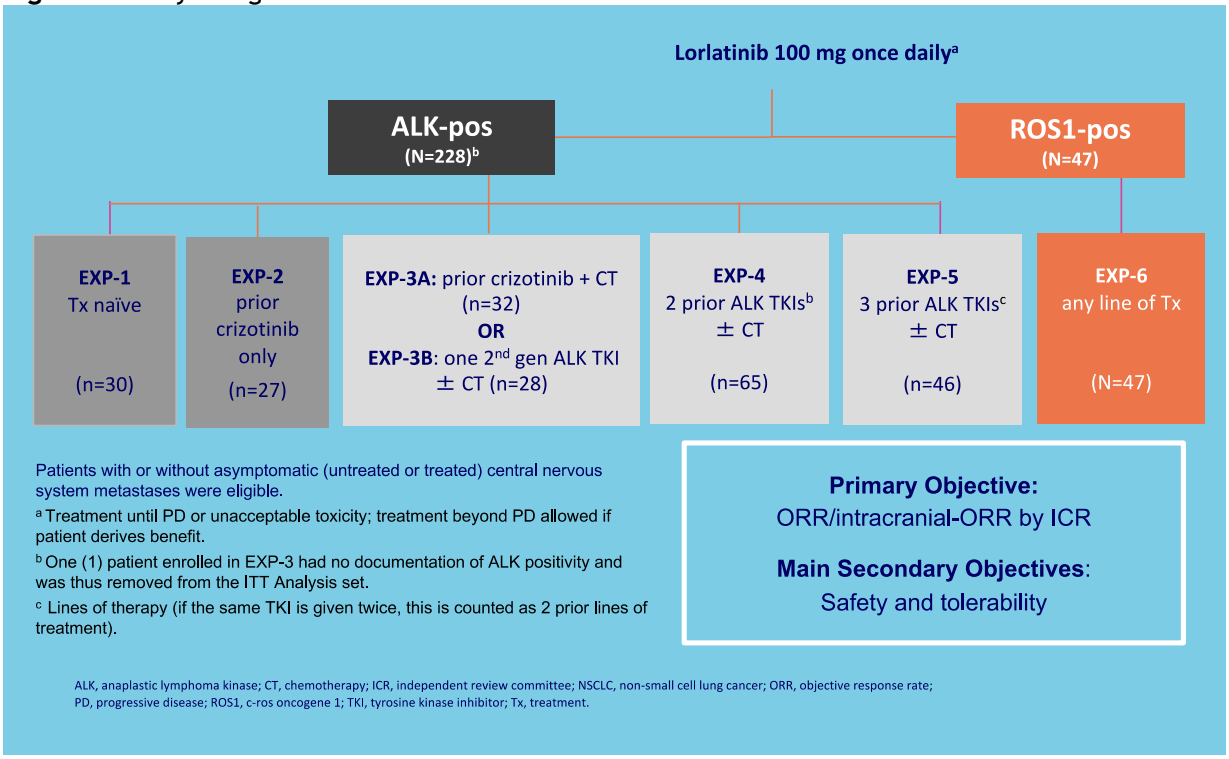
Study	NCT01970865
Treatment	Lorlatinib
Primary outcomes	Objective response rate and intracranial objective response rate
Required sample size	According to the sponsor, the sample size of each cohort was based on an estimation design with no specific hypothesis testing. [2] The sponsor clarified that when the study first started, data were available only for activity of other ALK TKIs after crizotinib, not for the other cohorts that the sponsor tested; thus, the study was based on a simple estimation design to evaluate activity of lorlatinib in the different prior treatment settings. Therefore, the sample size of EXP 3B, EXP 4 and EXP 5 was not powered to detect statistical significance for the primary and secondary endpoints.[7]
Sample size	• EXP 3 was split into EXP 3A and EXP 3B. EXP 3B was comprised of patients that had been treated with one second generation ALK TKI only plus or minus chemotherapy[4] • Target enrolment for EXP 4 was set to 70 patients. Patients in EXP 4 and EXP 5 were exposed to 2-3 previous ALK TKIs plus or minus chemotherapy, most of which were crizotinib and one or two second generation ALK TKIs.[2] • EXP 5 and EXP 6 were set targets of 40 patients each (see Figure 2 below)
Allocation	The study was not randomized.[3]
Masking	The study was not blinded.[3]
Final analysis	The estimated study completion date is August 19, 2020.[13]
Ethics Approval	Yes. The protocol was approved by the institutional review board or independent ethics committee at each participating centre.[2]

a) Trials

One non-randomized, phase II, ongoing, multicentre, open-label, single-arm study (Trial 1001) met the inclusion criteria. The aim of this study was to investigate the activity of single-agent lorlatinib in patients with ALK-positive, advanced, NSCLC.[2] This study was

funded by Pfizer. All authors, some employed by Pfizer contributed towards the interpretation of the data as well as the development and approval of the manuscript. Complete access to the data was available to all study authors and the corresponding author had authority to submit the publication. This study enrolled 276 patients between September 15, 2015 and October 3, 2016 across 47 centres from 14 countries which included Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Singapore, Spain, Switzerland, Taiwan, and United States (US). [3] [4]Randomization was not performed. The cohort of patients that were treated in the following cohorts: EXP 3B, EXP 4 and EXP 5 aligns with the reimbursement indication and results for these cohorts will be reported. The March 15, 2017 data cut off represents the actual study completion date. According to the sponsor, ad-hoc updated analyses were conducted with the data cut off February 2, 2018.[7] The study design is outlined in Figure 1.[4]

Figure 2 Study design of cohorts[4]



The primary efficacy outcome was objective response rate which includes confirmed complete response (CR) or partial response (PR) and intracranial tumour response assessed according to modified Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.[2] Up to five CNS target lesions were permitted and measured by independent central radiology review (ICR) in pooled cohorts of ALK-positive patients. [31]

Secondary outcomes included the following:

Duration of response was defined as the time from the first documented objective tumour response (either CR or PR) to the first documented disease progression or death from any cause based on independent central review and investigator assessments.[31]

Time to first tumour response was defined as the time from first dose to first documentation of objective tumour response (CR or PR). In the event objective response proceeds from PR to CR, PR was recorded as the onset of response.[31] Both independent central review and investigator assessment assessed time to tumour response.

Progression free survival was defined as the time from first dose to first documented objective disease progression or death associated with the study based on independent central review.[31]Overall survival was defined as the time from first dose to the date of death. [31]

Time to tumour progression (TTP) was defined as the time from first dose to the date of the first documented objective tumor progression. In circumstances where tumour progression data included more than 1 date, the first date was used. [31] Intracranial TTP was defined as the time from first dose to the date of the first documented objective intracranial disease which was detected based on the following: new brain metastases or progression of existing brain metastases. [31]

Patient reported outcomes (PRO) were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and Lung Cancer Module (QLQ-LC13) (Version 3.0).[31] The EORTC QLQ-C30 is comprised of 30 questions which assessed the following five functional domains (physical, role, cognitive, emotional, and social), global quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. The QLQ-LC13 module outlined questions related to disease symptoms (dyspnea, cough, haemoptysis, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy, and alopecia), and analgesic use of lung cancer patients. A clinically meaningful change from baseline was defined as ≥ 10-point change within a treatment arm. An increase of ≥10 points in the average change from baseline was associated with improvement on the functioning and global QoL scales and worsening on the symptoms scale. The term stable was defined as a patient who neither improved nor worsened. [4,31] Data were collected from patients on day 1 of each 21-day cycle at the end of each treatment visit up to 38 cycles and then every other cycle. An instrument was considered complete if at least one item of the questionnaire was answered by the patient.[4]

Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and were assessed from the start of treatment until ≥28 days after the final lorlatinib dose. Assessments for safety were conducted on all patients (EXP 1-6) at baseline and each subsequent visit.[2]

Sample Sizes and Statistical analysis

The EXP 3 cohort was divided into EXP 3A and EXP 3B in which EXP 3B was analyzed separately.[2] Patients were pooled together in EXP 2 and EXP 3A because these patients had all been treated with crizotinib (first generation ALK TKI) as their only ALK TKI and prior chemotherapy compared to patients in EXP3B who were pre-treated with a second generation ALK TKI only. Patients in EXP 4 and EXP 5 were exposed to two or three previous ALK TKIs, most of which were crizotinib and one or two second generation ALK TKIs.

For the outcome of PFS, OS and DOR, the Kaplan-Meier method was applied to obtain the median event time and 95% confidence interval (CI) for the median.[3] Based on a request submitted to the sponsor, Kaplan-Meier curves for the cohorts EXP 3B, EXP 4-5 for the outcomes of PFS, OS and DOR were provided.

The safety analysis set included all patients (EXP 1-6) who received at least one dose of lorlatinib which included dose of lorlatinib administered on day 7.

The PRO-evaluable analysis set was defined as all enrolled patients who received at least one dose of lorlatinib and completed a PRO assessment during at least one post-baseline follow-up.[3] Scores obtained from the EORTC QLQ-C30 and the QLQ-LC13 were transformed on a scale of 0 to 100. Higher scores on the EORTC QLQ-C30 represented better levels of functioning and worse levels of symptoms. Higher scores on the EORTC QLQ-LC13 represented worse levels of symptoms.[31] Compliance rates for the EORTC QLQ-C30 and the QLQ-LC13 instruments were calculated at each time point as the number and proportion of patients that completed each instrument at each cycle up to 25 cycles.[31]

The ITT analysis set was comprised of patients with documented ALK gene rearrangement who were treated with at least 1 dose of lorlatinib.[3]

A summary of outcomes is outlined in table 6 and the corresponding statistical methods applied. Results for biomarker related endpoints were not reported.

Table 6. Statistical methods outlined for endpoints[3]

Endpoint	Statistical Method
ORR[a]	Percentage (2-sided 95% CI*)
IC ORR[a]	Percentage (2-sided 95% CI*)
TTR[a], IC TTR	Descriptive statistics; n (%)
DOR[a], IC DOR	K-M method (median and 2-sided 95% CI)*** Descriptive statistics; n (%)
PFS[a], OS	K-M method (median and 2-sided 95% CI)***
Probabilities of being event free/survival at 1 year and 18 months	K-M method (2-sided 95% CI**)
PROs	Descriptive statistics for absolute scores and change from baseline of the EORTC QLQ-C30 and QLQ-LC13 multiple-item and single-item scale scores
Biomarker related endpoints	Outlined in Study 1001 SAP Section 6.3.4

Source: Study 1001 Statistical Analysis Plan Version 5.
*Using exact method based on binomial distribution.
**Using the normal approximation to the log-transformed cumulative hazard function.
*** Confidence intervals for the median and quartiles using the method of Brookmeyer and Crowley.
a. Based on ICR and Investigator assessment.
Abbreviations: CI=confidence interval; CNS=central nervous system; DOR=duration of response; K-M=Kaplan-Meier; IC=intracranial; ICR=Independent Central Review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QLQ-LC13=Quality of Life Questionnaire Lung Cancer 13; SAP=Statistical Analysis Plan; TTR=time to tumour response.

There was a total of 276 major protocol deviations in the following categories: inclusion criteria, concomitant treatment, safety reporting, informed consent and other. The highest proportion of protocol deviations were committed in the category of inclusion criteria (n=54, 19.6%). Table 7 outlines protocol deviations.[3]

Table 7. Important protocol deviations in Phase 2[3]

Protocol Deviation Category	Protocol Deviation Subcategory	Total (N=276) n (%)
Inclusion criteria	No archival tissue available or no de novo biopsy performed	8 (2.9)
	ALK/ROS1 status not confirmed	1 (0.4)
	ALK/ROS1 testing method not per protocol	14 (5.1)
	Did not meet all other inclusion criteria	31 (11.2)
Concomitant treatment	Anti-cancer therapy administered prior to documented PD	1 (0.4)
Safety reporting	SAE delayed or not reported to sponsor	12 (4.3)
Informed consent	Required informed consent not obtained on time	6 (2.2)
Other	Special safety concern letter not relayed to patient in a timely manner	2 (0.7)

Source: Table 14.1.1.4.2.
Abbreviations: ALK =anaplastic lymphoma kinase; N/n=number of patients; SAE=serious adverse event

a) ***Populations***

For this review, EXP 3B, EXP 4 and EXP 5 have been identified as relevant cohorts. Among 276 patients enrolled from across 14 countries and 47 sites, there were 7 patients enrolled from Canada.[5] The ITT population comprised of EXP 3B, EXP 4-5 included 139 patients of which 41 patients were remaining on lorlatinib and 98 patients discontinued treatment.[3] The median age of patients in EXP 3B and EXP 4-5 were 54 years old and 51 years old respectively. The proportion of female patients were similar in EXP 3B and EXP 4-5. The majority of patients were white or of Asian ethnicity and had an ECOG PS of 0 or 1. There were 13 patients (46%) in EXP 3B and 83 patients (75%) in EXP 4-5 with brain metastases present at baseline. All 28 patients (100%) in the EXP 3B cohort received one previous ALK TKI regimen. In EXP 4-5, 65 patients (59%) received two previous ALK TKI regimens whereas 42 patients (38%) received 3 prior ALK TKI regimens. The patient demographics and baseline disease characteristics of all enrolled patients are presented in Table 8.

Table 8: Patient demographics and baseline disease characteristics[4]

Characteristics	Previous 2nd-gen ALK TKI +/- chemotherapy (EXP3B; n=28)	≥ 2 previous ALK TKIs* +/- chemotherapy (EXP4-5; n=111)	Pooled safety group (EXP1-6; n=275)
Age, years			
Median	54.0	51.0	54.0
Mean (SD)	55.0 (11.6)	51.9 (11.5)	53.6 (12.1)
Range	33-77	29-83	19-85
Women, n (%)	16 (57%)	62 (56%)	157 (57%)
Race, n (%)			
White	7 (25%)	59 (53%)	132 (48%)
Asian	16 (57%)	37 (33%)	103 (37%)
Other	2 (7%)	5 (5%)	15 (5%)
Unspecified	3 (11%)	10 (9%)	25 (9%)
ECOG PS, n (%)			
0	15 (54%)	46 (41%)	119 (43%)
1	13 (46%)	59 (53%)	146 (53%)
2	0	6 (5%)	10 (4%)
Brain metastases† at baseline, n (%)	13 (46%)	83 (75%)	166 (60%)
Number of brain metastases† at baseline			
1-3	4 (31%)	34 (41%)	65 (39%)
4-6	6 (46%)	25 (30%)	56 (34%)
7-9	3 (23%)	14 (17%)	28 (17%)

Characteristics	Previous 2nd-gen ALK TKI +/- chemotherapy (EXP3B; n=28)	≥ 2 previous ALK TKIs* +/- chemotherapy (EXP4-5; n=111)	Pooled safety group (EXP1-6; n=275)
≥ 10	0	10 (12%)	17 (10%)
Median	6	4	5
Previous radiotherapy, n (%)	12 (43%)	83 (75%)	154 (56%)
Previous brain-directed radiotherapy, n (%)	8 (29%)	59 (53%)	103 (37%)
Number of previous chemotherapy regimens, n (%)			
0	15 (54%)	26 (23%)	105 (38%)
1	10 (36%)	43 (39%)	96 (35%)
2	2 (7%)	26 (23%)	43 (16%)
3	1 (4%)	8 (7%)	22 (8%)
≥ 4	0	8 (7%)	9 (3%)
Number of previous ALK TKI regimens, n (%)			
0	0	0	43 (16%)
1	28 (100%)	0	117 (43%)
2	0	65 (59%)	67 (24%)
3	0	42 (38%)	44 (16%)
≥ 4	0	4 (4%)	4 (1%)

b) Interventions

Lorlatinib was administered orally in a tablet form at a starting dose of 100 mg once daily continuously for 21-day cycles. Treatment continued until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients were allowed to continue treatment with lorlatinib after objective progression as long as there was evidence of clinical benefit in the investigator's opinion.[2] According to the sponsor, clinical benefit was defined as the primary tumor and potential metastases under the treatment of lorlatinib being under better control as opposed to the treatment being completely discontinued. Specifically, objective progression that does not result in deterioration, worsened symptoms, but managed with supportive therapy and controlled brain metastasis with progression elsewhere.[7] Toxicities were managed using dose delays and reductions based on investigator discretion.[2] The first dose reduction was 75 mg lorlatinib orally followed by a second dose reduction of 50 mg orally. Patients who were unable to tolerate 50 mg lorlatinib orally were permanently discontinued from treatment.[28] Based on the safety analysis set, there were 8 patients (28.6%) in EXP 3B, 15 patients (23.1%) in EXP 4 and 10 patients (21.7%) in EXP 5 that required one dose reduction to 75 mg QD.[7] For reasons other than treatment-related toxicity that continued for >1 week which led to treatment interruptions, patients were permitted to resume treatment in consultation with the sponsor.

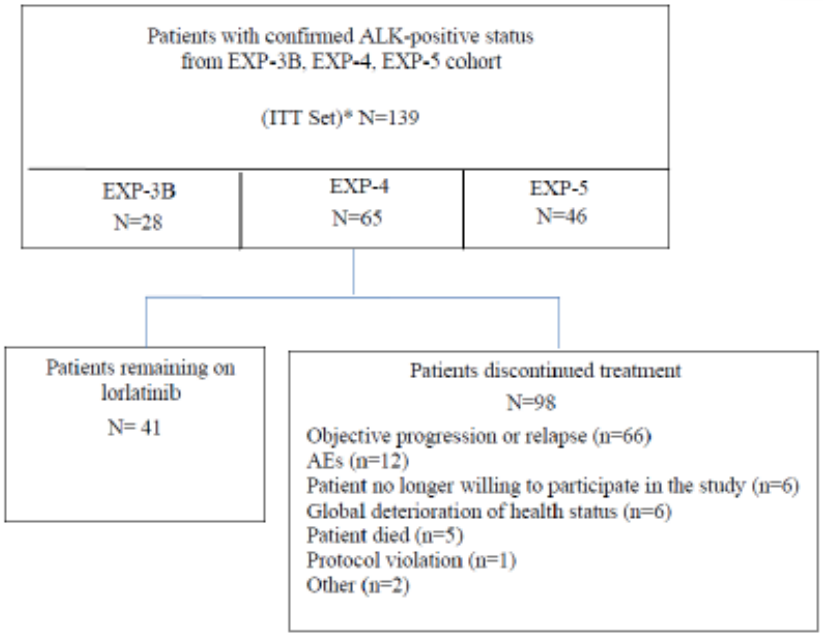
At the February 2, 2018 data cut-off, there were 64/65 patients (98.5%) and 46 patients (100%) in EXP 4 and EXP 5 respectively that received concomitant medications. It is unclear the proportion of EXP 3B that received concomitant medications.[6] The concurrent use of strong/moderate CYP3A4 leads to a potential increase in lorlatinib toxicities and may inhibit lorlatinib metabolism. The most frequently used concomitant drugs (used by >30 patients) were atorvastatin, dexamethasone, fenofibrate, furosemide, ibuprofen, lorazepam, omeprazole, paracetamol, potassium chloride, pravastatin, pravastatin sodium, prednisone, rosuvastatin, rosuvastatin calcium, and sennoside A+B.[7] In addition, strong CYP3A4 inducers (e.g., phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort) concurrently with lorlatinib may create reduced plasma concentrations and is not permitted from 12 days prior to the first dose of lorlatinib until study treatment discontinuation.[6] Severe hepatoxicity is also associated with the concurrent use of lorlatinib.[28] Due to the inhibition of CYP2C9 (in vitro) by lorlatinib, the concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices (e.g., warfarin, phenytoin or celecoxib) combined with lorlatinib is not permitted. Due to the inhibition of CYP2B6 (in vitro) by lorlatinib, the concurrent use of drugs that are CYP2B6 substrates (e.g., bupropion and efavirenz) combined with lorlatinib is not permitted. Similarly, CYP3A4 substrates and P-gp is inhibited by lorlatinib and the concurrent use of CYP3A4 substrates with lorlatinib and P-gp with lorlatinib is not permitted.[6]

At the February 2, 2018 data cut-off, 61 patients received a total of 106 subsequent therapies which included crizotinib, alectinib, brigatinib, ceritinib, platin (cisplatin or carboplatin), pemetrexed, immunotherapy or other (e.g., gemcitabine, taxol, lorlatinib and investigational products). There were 24 patients (39.3%) that received either cisplatin or carboplatin followed by 23 patients (37.7%) that received pemetrexed.[7]

b) ***Patient Disposition***

At the data cut off February 2, 2018, among the 139 patients in the ITT EXP 3B, EXP 4 and EXP 5 cohorts, 98 patients discontinued treatment. The following reasons for exclusions were outlined: objective progression or relapse (n=66), AEs (n=12), patient no longer willing to participate in the study (n=6), global deterioration of health status (n=6), patient died (n=5), protocol violation (n=1), other (n=2). Details are outlined in Figure 2.

Figure 3. Study Flow Chart for EXP3B, EXP4, EXP5 (data cut off February 2, 2018)[3]



* ITT set = Includes Patient 10022026 for whom confirmed ALK-positive status became available after 15 March 2017
Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; ITT=intention to treat; N/n=number of subjects.

d) Limitations/Sources of Bias

There are limitations associated with the study design and methodology of Trial 1001.

- Firstly, this phase II trial is comprised of several cohorts and only EXP 3B, EXP 4 and EXP 5 were of interest for this review. A pooled analysis plan for EXP 3B-5 was not outlined a priori in the protocol.
- A single arm clinical trial was conducted; thus, comparative effectiveness cannot be assessed.
- The sample sizes of EXP 3B, EXP 4 and EXP 5 were not powered to detect statistical significance for the primary and secondary endpoints.[7] Therefore, the interpretation of these results is limited.

The sponsor provided feedback on the pERC Initial Recommendation and disagreed with the interpretation that the results of Trial 1001 are only hypothesis generating. The sponsor stated that the EXP 3B-5 cohorts had the robustness to justify lorlatinib's conditional approval from Health Canada. In response to the sponsor's feedback, the Methods team confirmed that the trial publication stated that the sample size of each cohort was based on an estimation design with no specific hypothesis testing.[2] The sponsor clarified at the Checkpoint meeting that when the study first started, data were available only for activity of other ALK TKIs after crizotinib, not for the other cohorts that the sponsor tested; thus the study was based on a simple estimation design to evaluate activity of lorlatinib in the different prior treatment settings. Therefore, the sample size of EXP 3B, EXP 4 and EXP 5 was not powered to detect statistical significance for the primary and secondary endpoints.[7]

- Methods for testing for multiplicity were not outlined in the protocol for primary and secondary endpoints.
- Results related to patient-reported outcomes were descriptive only. It is unclear the characteristics of patients that did not complete the EORTC QLQ C30 at baseline and whether these patients may have responded differently to patients that did not complete the questionnaire.
- Approximately 20% of major protocol deviations were attributed to inclusion criteria which suggests a possible selection bias and implications on sample sizes of the cohorts.
- Safety data were presented across all cohorts (EXP 1-6) however, EXP 3B-5 was of interest for this review. No statistical tests were performed to determine if the proportion of adverse events, grade 3 and 4 adverse events were statistically different between the unpooled analysis and pooled analysis for EXP 3B-5. It is possible some cohorts may have driven the higher proportion of adverse events in the unpooled analysis.
- Due to the sponsor involved in various aspects of the trial (e.g., data interpretation, development and approval of manuscript), there is a possible conflict of interest.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Objective Response Rate (ORR)-Independent Central Review

At the data cut off-of March 15, 2017, the median duration of follow-up was 7.0 months (95% CI 5.6-12.7) in EXP 3B and 7.2 months (95% CI 6.9-7.2) in EXP 4-5.[2] There were 9 patients (32.1%, 95% CI 15.9-52.4) and 43 patients (38.7%, 95% CI 29.6-48.5) had a confirmed ORR in EXP 3B and EXP 4-5 respectively.[2] One patient (3.7%) in EXP 3B and two patients (1.8%) in EXP 4-5 had a CR.[3] Eight patients (29.6%) in EXP 3B and 41 patients (36.9%) in EXP 4-5 had a PR. Results are presented in Table 9.

Table 9. Best overall response based on ICR in patients with ALK-positive NSCLC-ITT population in EXP cohorts (data cut-off March 15, 2017)[3]

Variable	EXP-3B (N=27)	EXP-4:EXP-5 (N=111)	EXP-2:EXP-3A (N=59)
Objective response rate [CR + PR], n (%)	9 (33.3)	43 (38.7)	41 (69.5)
95% exact CIa	(16.5, 54.0)	(29.6, 48.5)	(56.1, 80.8)
Best overall response, n (%)			
Complete response (CR)	1 (3.7)	2 (1.8)	1 (1.7)
Partial response (PR)	8 (29.6)	41 (36.9)	40 (67.8)
Stable/no response	10 (37.0)	38 (34.2)	10 (16.9)
Objective progression	6 (22.2)	20 (18.0)	6 (10.2)

At the data cut-off of February 2, 2018, the median follow-up was 9.9 months (EXP 4-5).[3] The ORR was 42.9% (95% CI 24.5-62.8) in EXP 3B, 41.5% (95% CI 29.4-54.4) in EXP 4 and 37.0% (95% CI 23.2-52.5) in EXP5. One patient (3.6%) in EXP 3B and 2 patients (1.8%) in EXP 4-5 had a CR. Eleven patients (39.3%) in EXP 3B and 42 patients (37.8%) in EXP 4-5 had a PR. Results are shown in Table 10.

Table 10. best overall response based on ICR in patients with ALK-positive NSCLC-ITT population in EXP cohorts (data cut-off February 2, 2018)[3]

Data cutoff: 02 Feb 2018	EXP-3B (N=28)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-4:EXP-5 (N=111)	EXP-3B:EXP-5 (N=139)
ORR [CR+PR]	**12 (42.9)**	**27 (41.5)**	**17 (37.0)**	**44 (39.6)**	**56 (40.3)**
95% exact CI[a]	(24.5, 62.8)	(29.4, 54.4)	(23.2, 52.5)	(30.5, 49.4)	(32.1, 48.9)
Best overall response					
CR	1 (3.6)	2 (3.1)	0	2 (1.8)	3 (2.2)
PR	11 (39.3)	25 (38.5)	17 (37.0)	42 (37.8)	53 (38.1)
Stable/no response	8 (28.6)	22 (33.8)	15 (32.6)	37 (33.3)	45 (32.4)
Objective progression	6 (21.4)	10 (15.4)	10 (21.7)	20 (18.0)	26 (18.7)
Indeterminate	2 (7.1)	6 (9.2)	4 (8.7)	10 (9.0)	12 (8.6)

At the data cut-off March 15, 2017 for intracranial ORRs, 5 patients (55.6%), 95% CI 21.2-86.3 and 26 patients (53.1%), 95% CI 38.3-67.5 had a confirmed ORR in EXP 3B and EXP 4-5 respectively.[2] One patient (11.1%) in EXP 3B and 10 patients (20.4%) in EXP 4-5 had a CR. Four patients (44.4%) in EXP 3B and 16 patients (32.7%) in EXP 4-5 had a PR. Results are shown in Table 11.

At the data cut off-of February 2, 2018 for intracranial ORRs, 6 patients (66.7%), 95% CI 29.9-92.5 and 25 patients (52.1%), 95% CI 37.2-66.7 had a confirmed ORR in EXP 3B and EXP 4-5 respectively. Two patients (22.2%) in EXP 3B and 10 patients (20.8%) in EXP 4-5 had a CR. Four patients (44.4%) in EXP 3B and 15 patients (31.3%) in EXP 4-5 had a PR.

Table 11. Best overall intracranial response based on ICR assessment in patients with ALK positive NSCLC and brain metastases with at least 1 measurable lesion – ITT population in EXP cohorts[3]

Data cutoff: 02 Feb 2018	EXP-3B (N=9)	EXP-4 (N=24)	EXP-5 (N=24)	EXP-4:EXP-5 (N=48)	EXP-3B:EXP-5 (N=57)
ORR (CR + PR) n (%)	6 (66.7)	14 (58.3)	11 (45.8)	25 (52.1)	31 (54.4)
95% exact CI[a]	(29.9, 92.5)	(36.6, 77.9)	(25.6, 67.2)	(37.2, 66.7)	(40.7, 67.6)
Best Overall Response n (%)					
CR	2 (22.2)	6 (25.0)	4 (16.7)	10 (20.8)	12 (21.1)
PR	4 (44.4)	8 (33.3)	7 (29.2)	15 (31.3)	19 (33.3)
Stable/no response	0	8 (33.3)	9 (37.5)	17 (35.4)	17 (29.8)
Objective progression	2 (22.2)	2 (8.3)	2 (8.3)	4 (8.3)	6 (10.5)
Indeterminate	1 (11.1)	0	2 (8.3)	2 (4.2)	3 (5.3)
Data cutoff: 15 Mar 2017	**EXP-3B (N=9)**	**EXP-4 (N=25)**	**EXP-5 (N=24)**	**EXP-4:EXP-5 (N=49)**	**EXP-3B:EXP-5[b]**
ORR (CR + PR) n (%)	5 (55.6)	16 (64.0)	10 (41.7)	26 (53.1)	-
95% exact CI[a]	(21.2, 86.3)	(42.5, 82.0)	(22.1, 63.4)	(38.3, 67.5)	-
Best Overall Response n (%)					
CR	1 (11.1)	6 (24.0)	4 (16.7)	10 (20.4)	-
PR	4 (44.4)	10 (40.0)	6 (25.0)	16 (32.7)	-
Stable/no response	0	7 (28.0)	10 (41.7)	17 (34.7)	-
Objective progression	3 (33.3)	2 (8.0)	2 (8.3)	4 (8.2)	-
Indeterminate	1 (11.1)	0	2 (8.3)	2 (4.1)	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.1.2.3.1.2.1.ema
15 Mar 2017: Module 5.3.5.3 D120 Supporting Table 14.2.2.1.1.2.1.2.1.t; Table 14.2.2.1.2.2.1.2.1.t.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; EXP=expansion; ICR=Independent Central Review; ITT=intention-to-treat; N/n=number of patients; NSCLC=non-small cell lung cancer; ORR=objective response rate; PR=partial response; SCE=Summary of Clinical Efficacy.

a. Using exact method based on binomial distribution.
b. Data (15 March 2017 data cutoff) were not provided before.

Duration of Response (DOR)-Independent Central Review

At the March 15, 2017 data cut-off, the median duration of response was not reached in either the EXP 3B (95% CI 4.1-NR) and EXP 4-5 (95% CI 5.5-NR) cohorts.[3] The median duration of follow-up for response was 7.0 months (IQR 5.6-8.3) in EXP 3B and 7.2 months (IQR 5.6-9.8) in EXP 4-5.[2]

At the February 2, 2018 data cut-off, the median duration of response in the EXP 3B cohort was 5.6 months (95% CI 4.2, NR) and 9.9 months in EXP 4-5 (95% CI 5.7, 24.4).[4]

At the March 15, 2017 data cut-off, the median duration of intracranial response was not reached in the EXP 3B (95% CI 4.1- NR) and 14.5 months in EXP 4-5 (95% CI 6.9 –14.5).[3]

At the February 2, 2018 data cut-off, the median duration of intracranial response was not reached in the EXP 3B (95% CI 4.1- NR) and 12.4 months in EXP 4-5 (95% CI 6.0- NR). Results are presented in Table 12.[3] Figure 3 outlines the Kaplan-Meier curve for DOR.[7]

Table 12. ICR-assessed duration of intracranial response (objective responders only) – ITT population in EXP cohorts[3]

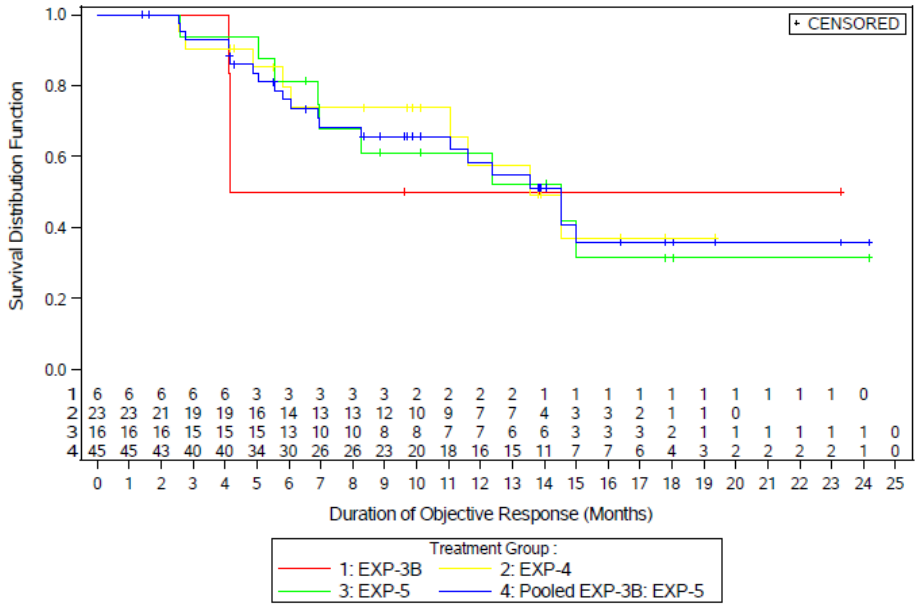
Data cutoff: 02 Feb 2018	EXP-3B (N=9)	EXP-4 (N=24)	EXP-5 (N=24)	EXP-4:EXP-5 (N=48)	EXP-3B:EXP-5 (N=57)
Patients with confirmed objective response (CR or PR), n	6	14	11	25	31
Median DOR (in months)	NR	11.1	12.4	12.4	12.4
95% CI[a]	(4.1, NR)	(5.8, NR)	(5.6, NR)	(6.0, NR)	(5.8, NR)
N (%) of patients with events (PD or death) among the responders	3 (50.0)	7 (50.0)	7 (63.6)	14 (56.0)	17 (54.8)
<3 months	0	2 (14.3)	1 (9.1)	3 (12.0)	3 (9.7)
3 to <6 months	3 (50.0)	2 (14.3)	2 (18.2)	4 (16.0)	7 (22.6)
6 to <9 months	0	1 (7.1)	2 (18.2)	3 (12.0)	3 (9.7)
9 to <12 months	0	1 (7.1)	0	1 (4.0)	1 (3.2)
12 to <15 months	0	1 (7.1)	2 (18.2)	3 (12.0)	3 (9.7)
N (%) of patients censored among the responders	3 (50.0)	7 (50.0)	4 (36.4)	11 (44.0)	14 (45.2)
<3 months	0	1 (7.1)	0	1 (4.0)	1 (3.2)
3 to <6 months	0	0	0	0	0
6 to <9 months	0	1 (7.1)	1 (9.1)	2 (8.0)	2 (6.5)
9 to <12 months	1 (16.7)	2 (14.3)	1 (9.1)	3 (12.0)	4 (12.9)
12 to <15 months	1 (16.7)	1 (7.1)	0	1 (4.0)	2 (6.5)
15 to <18 months	0	2 (14.3)	0	2 (8.0)	2 (6.5)
18 to <21 months	0	0	1 (9.1)	1 (4.0)	1 (3.2)
21 to <24 months	1 (16.7)	0	0	0	1 (3.2)
≥24 months	0	0	1 (9.1)	1 (4.0)	1 (3.2)
Data cutoff: 15 Mar 2017	**EXP-3B (N=9)**	**EXP-4 (N=25)**	**EXP-5 (N=24)**	**EXP-4:EXP-5 (N=49)**	**EXP-3B:EXP-5[b]**
Patients with confirmed objective response (CR or PR), n	5	16	10	26	-
Median DOR (in months)	NR (4.1, NR)	14.5	NR	14.5 (6.9, 14.5)	-
95% CI[a]	-	(6.0, 14.5)	(6.9, NR)	-	-
N (%) of patients with events (PD or death) among the responders	2 (40.0)	5 (31.3)	4 (40.0)	9 (34.6)	-
<3 months	0	2 (12.5)	1 (10.0)	3 (11.5)	-
3 to <6 months	2 (40.0)	1 (6.3)	1 (10.0)	2 (7.7)	-
6 to <9 months	0	1 (6.3)	2 (20.0)	3 (11.5)	-
9 to <12 months	0	0	0	0	-
12 to <15 months	0	1 (6.3)	0	1 (3.8)	-
N (%) of patients censored among the responders	3 (60.0)	11 (68.8)	6 (60.0)	17 (65.4)	
<3 months	0	2 (12.5)	0	2 (7.7)	-
3 to <6 months	2 (40.0)	2 (12.5)	1 (10.0)	3 (11.5)	-
6 to <9 months	0	4 (25.0)	4 (40.0)	8 (30.8)	-
9 to <12 months	0	2 (12.5)	0	2 (7.7)	-
12 to <15 months	1 (20.0)	1 (6.3)	1 (10.0)	2 (7.7)	-
15 to <18 months	0	0	0	0	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.8.3.2.4.2.1.ema; Table 14.2.2.7.3.2.4.2.1.ema.
15 Mar 2017: Module 5.3.5.3 D120 Supporting Tables 14.2.2.8.1.2.3.2.1.t; 14.2.2.8.2.2.3.2.1.t; 14.2.2.7.1.2.3.2.1.t; 14.2.2.7.2.2.3.2.1.t

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; DOR=duration of response; EXP=expansion; ICR=Independent Central Review; ITT=intention-to-treat; N/n=number of patients; NSCLC=non-small cell lung cancer; PD=progressive disease. PR=partial response.

a. Using Brookmeyer Crowley method.
b. Data (15 March 2017 data cutoff) were not provided before.

Figure 3. DOR intra-cranial ORR based on ICR -ITT population (data cut-off February 2, 2018)[7]



Time to tumour response (TTR)-ITT population

At the March 15, 2017 data cut-off, the median TTR was 1.4 months (1.3-3.0) and 1.4 months (1.2-9.9) in EXP 3B and EXP 4-5, respectively. The median IC TTR was 1.4 months (1.3-3.0) and 1.4 months (1.2-6.2) in EXP 3B and EXP 4-5, respectively.[3]

At the February 2, 2018 data cut-off, the median TTR was 1.4 months (range 1.2-16.6) in EXP 3B and 1.4 months (1.2-16.4) in EXP 4-5. The median IC TTR was 1.4 months (1.2-3.0) and 1.4 months (1.2-16.2) in EXP 3B and EXP 4-5, respectively.[3] Results are presented in Table 13.

Table 13. Time to tumour response in EXP cohorts – ITT population[3]

Data cutoff: 02 Feb 2018	EXP-3B	EXP-4	EXP-5	EXP-4:EXP-5	EXP-3B:EXP-5
Overall Response, N	12	27	17	44	56
Median TTR, months (range)	1.4 (1.2-16.6)	2.6 (1.2-16.4)	1.4 (1.2-9.3)	1.4 (1.2-16.4)	1.4 (1.2-16.6)
IC response,[a] N	6	14	11	25	31
Median IC TTR[a], months (range)	1.4 (1.2-3.0)	1.5 (1.2-16.2)	1.4 (1.2-10.6)	1.4 (1.2-16.2)	1.4 (1.2-16.2)
Data cutoff: 15 Mar 2017	**EXP-3B**	**EXP-4**	**EXP-5**	**EXP-4:EXP-5**	**EXP-3B:EXP-5[b]**
Overall Response, N	9	27	16	43	
Median TTR, months (range)	1.4 (1.3-3.0)	2.6 (1.2-9.9)	1.4 (1.2-4.0)	1.4 (1.2-9.9)	-
IC response, [a] N	5	16	10	26	-
Median IC TTR[a], months (range)	1.4 (1.3-3.0)	1.5 (1.2-6.2)	1.4 (1.2-3.3)	1.4 (1.2-6.2)	-

Source: **02 Feb 2018**: Module 5.3.5.3 D120 Supporting Table mo.171.2; Module 5.3.5.3 D120 Supporting Tables ema.233.feb.7; ema.233.feb.7.1.
15 Mar 2017: Module 5.3.5.2 Study 1001 CSR Supporting Tables 14.2.2.3.1.1.3.2.1; 14.2.2.3.2.1.3.2.1; Module 5.3.5.3 D120 Supporting Tables 14.2.2.3.2.2.3.2.1.t; 14.2.2.3.1.2.3.2.1.t.
Abbreviations: CSR=clinical study report; EXP=expansion; IC=intracranial; ITT=intention-to-treat; N=number of patients; TTR=time to tumor response.
a. In patients with at least 1 measurable CNS lesion.
b. Data (15 March data cutoff) were not provided before.

Progression Free Survival(PFS)-Independent Central Review

At the data cut-off March 15, 2017, the median PFS was 5.5 months (95% CI 2.9-9.0) in the EXP 3B and 6.9 months (95% CI 5.4-9.5) in EXP 4-5. There were ten patients (37.0%) censored in EXP 3B and 49 patients (44.1%) censored in EXP 4-5. The event free survival at 12 months was 29.3% (95% CI 11.9-49.3) and 31.9% (95% CI 21.2-43.1) in EXP 3B and EXP 4-5 respectively.[3] Figure 4 outlines the Kaplan-Meier curves for PFS (data cut-off March 15, 2017).

At the data cut off of February 2, 2018, the median PFS was 5.5 months (95% CI 2.9-8.2) in EXP 3B and 6.9 months (95% CI 5.4-9.5) among patients in EXP 4-5. There were 8 patients (28.6%) censored in EXP 3B and 34 patients (30.6%) censored in EXP 4-5. The event free survival at 12 months was 27.3% (95% CI 12.2-45.0) and 33.3% (95% CI 24.2-42.6) in EXP 3B and EXP 4-5 respectively. At 18 months, the event free survival was 21.9% (95% CI 8.1-39.9) and 23.1% (95% CI 15.2-32.0) in EXP 3B and EXP 4-5 respectively. [3] Results are displayed in Table 14. Figure 5 shows the updated Kaplan-Meier curve for PFS with the data cut-off February 2, 2018.

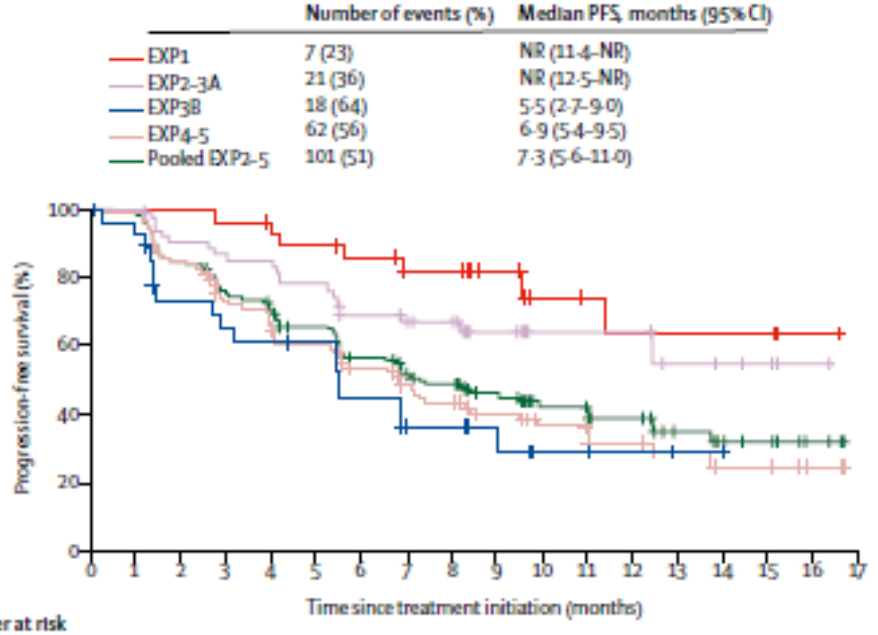
Table 14. PFS in patients with ALK-positive NSCLC – ITT population in EXP cohorts [3]

Data cutoff: 02 Feb 2018	EXP-3B (N=28)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-4:EXP-5 (N=111)	EXP-3B:EXP-5 (N=139)
Median Time to Event (months) 95% CI[a]	5.5 (2.9, 8.2)	7.4 (5.4, 11.1)	5.6 (4.0, 8.3)	6.9 (5.4, 9.5)	6.9 (5.4, 8.2)
Number with event, n (%)	20 (71.4)	44 (67.7)	33 (71.7)	77 (69.4)	97 (69.8)
Number censored, n (%)	8 (28.6)	21 (32.3)	13 (28.3)	34 (30.6)	42 (30.2)
% Probability of being event free at Month 12[b] (95% CI)[c]	27.3 (12.2, 45.0)	36.7 (24.6, 48.7)	28.3 (15.2, 42.9]	33.3 (24.2, 42.6)	32.1 (24.0, 40.3)
% Probability of being event free at Month 18[b] (95% CI)[c]	21.9 (8.1, 39.9)	27.1 (16.3, 39.0)	17.0 (7.1, 30.6)	23.1 (15.2, 32.0)	22.6 (15.5, 30.6)
Data cutoff: 15 Mar 2017	**EXP-3B (N=27)**	**EXP-4 (N=65)**	**EXP-5 (N=46)**	**EXP-4:EXP-5 (N=111)**	**EXP-3B:EXP-5[b]**
Median Time to Event (months) 95% CI[a]	5.5 (2.9, 9.0)	7.3 (5.4, 11.0)	5.6 (4.0, 12.5)	6.9 (5.4, 9.5)	-
Number with event, n (%)	17 (63.0)	36 (55.4)	26 (56.5)	62 (55.9)	-
Number censored, n (%)	10 (37.0)	29 (44.6)	20 (43.5)	49 (44.1)	-
% Probability of being event free at Month 12[c] (95% CI)[d]	29.3 (11.9, 49.3)	32.4 (19.3, 46.3)	36.0 (20.6, 51.6)	31.9 (21.2, 43.1)	-
% Probability of being event free at Month 18[c] (95% CI)[d]	-	-	-	-	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.5.2.1.1.2.1.ema.
15 Mar 2017: Module 5.3.5.2 Study 1001 CSR Supporting Tables 14.2.2.5.2.1.1.2.1; 14.2.2.5.1.1.1.2.1.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CSR=clinical study report; EXP=expansion; ITT=intention to treat; N/n=number of patients; NSCLC=non-small-cell lung cancer.
Note: The difference in number of patients in EXP-3B across the 2 data cutoffs was due to the positive ALK status confirmation for Patient 10022026 as of the 02 February 2018 data cutoff.

a. Based on the Brookmeyer Crowley Method.
b. Data (15 March 2017 data cutoff) were not provided before.
c. Estimated from the Kaplan-Meier curve.
d. Calculated using the normal approximation to the log transformed cumulative hazard rate.

Figure 4. Progression free survival outcomes (data cut-off March 15, 2017)

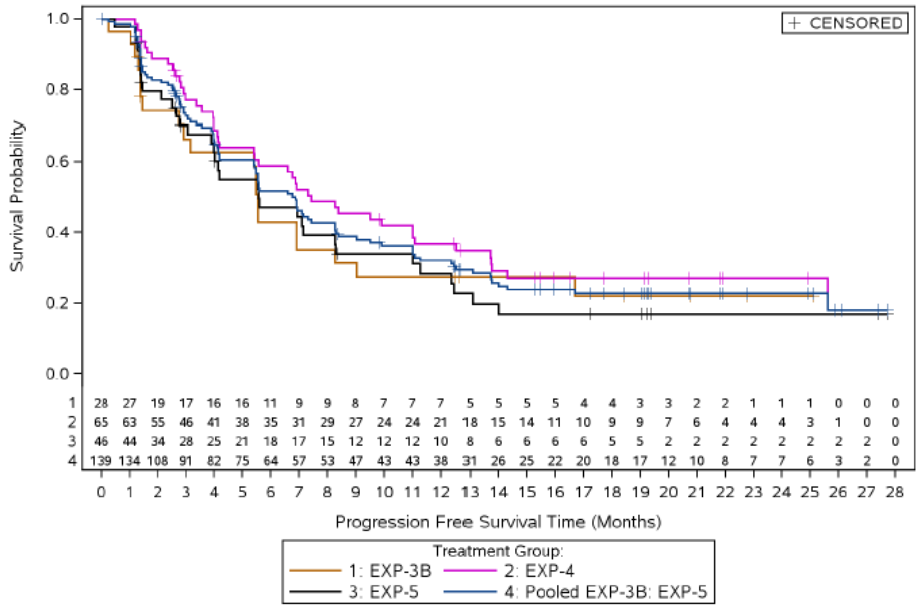


Number at risk (number censored)																		
EXP1	30	30	30	29	28	26	23	20	20	12	8	7	6	6	6	6	2	0
	(0)	(0)	(0)	(0)	(1)	(1)	(3)	(5)	(5)	(13)	(16)	(17)	(17)	(17)	(17)	(17)	(21)	(23)
EXP2–3A	59	59	53	50	49	44	31	28	26	14	9	9	9	5	4	3	1	0
	(0)	(0)	(0)	(1)	(1)	(2)	(10)	(12)	(14)	(25)	(30)	(30)	(30)	(33)	(34)	(35)	(37)	(38)
EXP3B	28	27	18	16	15	15	11	8	7	5	2	2	1	1	1	0	..	..
	(0)	(0)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(6)	(8)	(8)	(9)	(9)	(9)	(10)	..	..
EXP4–5	111	106	88	72	64	56	44	37	33	22	17	16	13	7	5	5	2	0
	(0)	(4)	(7)	(11)	(12)	(15)	(21)	(24)	(24)	(33)	(36)	(37)	(38)	(43)	(44)	(44)	(47)	(49)
Pooled EXP2–5	198	192	159	138	128	115	86	73	66	41	28	27	23	13	10	8	3	0
	(0)	(4)	(9)	(14)	(15)	(19)	(33)	(39)	(42)	(64)	(74)	(75)	(77)	(85)	(87)	(89)	(94)	(97)

Note: EXP1, EXP 2-3A are not relevant cohorts for this review.

Source: Reprinted from The Lancet Oncology, Vol 19. number 12, Solomon, B et al, Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, Pages 1654-1667, Copyright 2018, with permission from Elsevier.

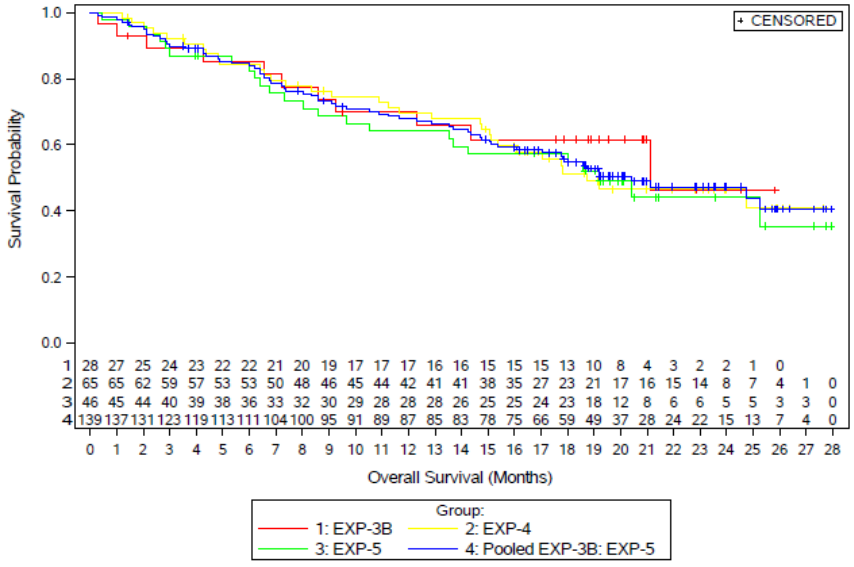
Figure 5. PFS-ITT population (data cut-off February 2, 2018) [7]



Overall Survival (OS)

The median duration of follow-up was approximately 20 months for EXP 3B-5. Among patients in EXP 3B and EXP 4-5, the median OS reached 21.1 months (95% CI: 12.3- NR) and 19.2 months (95% CI: 15.4- NR), respectively. For EXP 3B, 60.7% patients were still censored for OS. The OS for EXP 3B at 12 months was 69.8% (95% CI: 48.5- 83.6) and the OS at 18 months was 61.6% (95% CI: 40.2- 77.2). For EXP 4-5, a total of 55 (49.5%) patients were censored for OS. The OS for EXP 4-5 at 12 months was 67.3% (95% CI: 57.6- 75.4) and the OS at 18 months was 54.2% (95% CI: 44.0- 63.2).[3] Figure 6 outlines the updated OS data cut-off February 2, 2018.

Figure 6.OS -ITT population (data cut-off February 2, 2018)[7]



Time to Tumour Progression (TTP)

Based on independent assessment, the median TTP was 11 months (95% CI: 8.2- 13.7) overall. In cohort EXP 3, TTP was 9.0 months (95% CI: 5.5- NR), 8.4 months for cohort EXP 4 (95% CI: 5.6-13.7), and 7.1 months (95% CI: 4.1- 12.5) for cohort EXP 5.[3]

The median intracranial TTP was not reached for cohort EXP 3 and EXP 5 and 15.7 months (95%CI: 11.0- 15.7) for cohort EXP-4.[3]

Patient Reported Outcomes

At the data cut-off of March 15, 2017, there were 128 ALK-positive patients in the pooled EXP 3B-EXP 5 cohort /275 patients evaluable for PROs. A questionnaire was deemed complete provided at least one question was answered.[4] The EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were administered each cycle up to 24 cycles. According to the PRO analysis set, the completion rates were high up to cycle 24.[4] Completion rates was not available for EXP 3B only.

Improved was defined as a ≥10-point increase from baseline and worse was defined as a ≥10-point decrease from baseline. Stable was defined as a patient who neither improved nor worsened.[4] The results showed that 49 patients (38.3%) showed improvement on the global QoL EORTC QLQ- C30, 49 patients (38.3%) were stable and 30 patients (23.4%) demonstrated worsening symptoms.

On the EORTC QLQ-C30, the highest improvement from baseline was observed for role functioning among 50 patients (39.1%) followed by 33.6% for emotional functioning. From baseline, 74 patients (57.8%) of patients showed stable cognitive function. whereas 47 patients (25.5%) demonstrated worse cognitive functioning.

Across the symptom scales of the EORTC QLQ-C30, from baseline, the highest improvement was for fatigue among 62 patients (48.4%) followed insomnia and appetite loss among 59 patients (46.1%) for each scale. From baseline, nausea and vomiting was stable among 86 patients (67.2%), diarrhea (65.6%) for 84 patients and constipation (61.7%) for 79 patients. From baseline, a worsening of symptoms was observed for dyspnea (23.4%).

On the QLQ-LC13 symptoms scale, the highest improvement from baseline observed for cough was among 53 patients (41.4%), 41 patients (32.0%) for pain in other parts and dyspnea among 39 patients (30.5%). From baseline, haemoptysis was stable among 109 patients (85.2%) and dysphagia (78.9%) for 101 patients. From baseline, while peripheral neuropathy was stable among 67 patients (52.3%), there was a worsening in symptoms among 48 patients (37.5%). Results are outlined in table 15.

Table 15. Change from Baseline in EORTC QLQ-C30 and QLQ-LC13 Scales in the PRO-Evaluable Analysis Set (Pooled EXP 3B-5) (data cut-off March 15, 2017)[4]

EORTC QLQ-C30 and QLQ-LC13 Scales	Items	Improved	Stable	Worsening
Global QoL (QLQ-C30)	Global QoL	49 (38.3%)	49 (38.3%)	30 (23.4%)
Functional scales (QLQ-C30)	Physical functioning	39 (30.5%)	67 (52.3%)	24 (13.0%)
	Role functioning	50 (39.1%)	45 (35.2%)	36 (19.6%)
	Emotional functioning	43 (33.6%)	68 (53.1%)	20 (10.9%)
	Cognitive functioning	25 (19.5%)	74 (57.8%)	47 (25.5%)
	Social functioning	39 (30.5%)	64 (50.0%)	25 (13.6%)
Symptom scales (QLQ-C30)	Fatigue	62 (48.4%)	44 (34.3%)	22 (17.2%)
	Nausea and vomiting	34 (26.6%)	86 (67.2%)	8 (6.3%)
	Pain	49 (38.3%)	58 (45.3%)	21 (16.4%)
	Dyspnea	42 (32.8%)	56 (43.8%)	30 (23.4%)
	Insomnia	59 (46.1%)	51 (39.8%)	18 (14.1%)
	Appetite loss	59 (46.1%)	64 (50.0%)	5 (3.9%)
	Constipation	29 (22.7%)	79 (61.7%)	20 (15.6%)
	Diarrhea	24 (18.8%)	84 (65.6%)	20 (15.6%)
Symptom scales (QLQ-LC13)	Dyspnea	39 (30.5%)	61 (47.7%)	27 (21.1%)
	Cough	53 (41.4%)	56 (43.8%)	18 (14.1%)
	Haemoptysis	12 (9.4%)	109 (85.2%)	6 (4.7%)
	Sore mouth	13 (10.2%)	92 (71.9%)	22 (17.2%)
	Dysphagia	13 (10.2%)	101 (78.9%)	13 (10.2%)
	Peripheral neuropathy	12 (9.4%)	67 (52.3%)	48 (37.5%)
	Alopecia	20 (15.6%)	83 (64.8%)	24 (18.8%)
	Chest pain	38 (29.7%)	73 (57.0%)	16 (12.5%)
	Pain in arm or shoulder	32 (25.0%)	71 (55.5%)	24 (18.8%)
	Pain in other parts	41 (32.0%)	45 (35.2%)	40 (31.3%)

Data are n (%). For functioning and global QoL, "improved" was defined as a ≥10-point increase from baseline and "worsening" was defined as a ≥10-point decrease from baseline. "Stable" was defined as a patient who neither improved nor worsened. For symptoms, "improved" was defined as a ≥10-point decrease from baseline and "worsening" was defined as a ≥10-point increase from baseline. ALK=anaplastic lymphoma kinase; EORTC=European Organisation for the Research and Treatment of Cancer; EXP=expansion cohort; PRO=patient-reported outcomes; QLQ-C30=Quality of Life Questionnaire–Core 30; QLQ-LC13=Quality of Life Questionnaire Lung Cancer Module; QoL=quality of life; TKI=tyrosine kinase inhibitor.

Safety Outcomes

At the March 15, 2017 data cut-off, in the safety analysis set of 275 patients, patients received 100 mg QD in 21-day cycles. Hypercholesterolemia was the most common treatment related adverse event that occurred in 224 patients (81%) followed by hypertriglyceridemia among 166 patients (60%), oedema in 119 patients (43%) and peripheral neuropathy among 82 patients (30%). The most commonly reported Grade 3-4 treatment related adverse event was hypercholesterolemia and hypertriglyceridemia which occurred in 43 patients (16%) each. Serious treatment-related adverse events across all grades occurred in 19 (7%) of 275 patients. Cognitive effects were the most common serious treatment related adverse event which occurred in 2 patients (0.7%).[5] There were

7 patients (3%) that discontinued due to treatment-related adverse events. Reasons for permanent discontinuation from the study included affect lability, cognitive disorder, confusional state, hallucination (auditory/visual), hydrocephalus, leukocytosis, pneumonitis and tinnitus. [5]

Table 16. Treatment-related adverse events in patients treated with lorlatinib (all cohorts: EXP1–6)[2]

	Grade 1–2	Grade 3	Grade 4
Hypercholesterolaemia*	181 (66%)	39 (14%)	4 (1%)
Hypertriglyceridaemia*	123 (45%)	36 (13%)	7 (3%)
Oedema*	113 (41%)	6 (2%)	0
Peripheral neuropathy*	77 (28%)	5 (2%)	0
Weight increased	45 (16%)	5 (2%)	0
Cognitive effects*	46 (17%)	3 (1%)	0
Mood effects*	39 (14%)	2 (1%)	0
Fatigue*	35 (13%)	1 (<1%)	0
Diarrhoea	28 (10%)	1 (<1%)	0
Arthralgia	28 (10%)	0	0
AST increased	27 (10%)	1 (<1%)	0
Dizziness	23 (8%)	2 (1%)	0
ALT increased	22 (8%)	2 (1%)	0
Speech effects*	19 (7%)	1 (<1%)	0
Lipase increased	10 (4%)	7 (3%)	1 (<1%)
Anaemia	13 (5%)	2 (1%)	0
Amylase increased	12 (4%)	2 (1%)	0
Rash	13 (5%)	1 (<1%)	0
Vomiting	11 (4%)	1 (<1%)	0
Dyspnoea	8 (3%)	1 (<1%)	0
Hypertension	4 (1%)	4 (1%)	0
Ejection fraction decreased	5 (2%)	1 (<1%)	0
Hyperglycaemia	4 (1%)	2 (1%)	0
Localised oedema	4 (1%)	2 (1%)	0
Hallucination, auditory	4 (1%)	1 (<1%)	0
Abdominal pain	3 (1%)	1 (<1%)	0
Hypophosphataemia	2 (1%)	2 (1%)	0
Hypoxia	1 (<1%)	2 (1%)	0
Night sweats	2 (1%)	1 (<1%)	0
(Table 3 continues in next column)			

	Grade 1–2	Grade 3	Grade 4
(Continued from previous column)			
Pulmonary oedema	2 (1%)	1 (<1%)	0
Acute respiratory failure	0	1 (<1%)	1 (<1%)
Hyponatraemia	1 (<1%)	1 (<1%)	0
Presyncope	1 (<1%)	1 (<1%)	0
Respiratory failure	0	2 (1%)	0
Ascites	0	1 (<1%)	0
Blood potassium increased	0	0	1 (<1%)
Diabetes mellitus	0	1 (<1%)	0
Erysipelas	0	1 (<1%)	0
Gastritis	0	1 (<1%)	0
Glossitis	0	1 (<1%)	0
Hydrocephalus	0	1 (<1%)	0
Hypermagnesaemia	0	1 (<1%)	0
Interstitial lung disease	0	1 (<1%)	0
Leukocytosis	0	1 (<1%)	0
Mental status changes	0	1 (<1%)	0
Mucocutaneous candidiasis	0	1 (<1%)	0
Pancreatitis	0	1 (<1%)	0
Pneumonia	0	1 (<1%)	0
Pneumonitis	0	0	1 (<1%)
Thrombosis	0	1 (<1%)	0

Data are n (%). This table lists treatment-related adverse events reported in at least 10% of patients and all grade 3–4 treatment-related adverse events. No grade 5 treatment-related adverse events were reported. ALT=alanine aminotransferase. AST=aspartate aminotransferase. EXP=expansion cohort. * Cluster term comprising adverse events that represent similar clinical symptoms or syndromes.

Table 3: **Treatment-related adverse events in patients treated with lorlatinib (all cohorts: EXP1–6)**

Source: Reprinted from The Lancet Oncology, Vol 19. number 12, Solomon, B et al, Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, Pages 1654-1667, Copyright 2018, with permission from Elsevier.

In the pooled EXP 3B-5 cohort (data cut-off February 2, 2018), any Grade 3 and Grade 4 adverse event was reported in 51 patients (36.7%) and 9 patients (6.5%) respectively. Grade 3 and Grade 4 hypercholesterolemia occurred in 19 patients (13.7%) and 1 patient (0.7%) respectively. In addition, Grade 3 and Grade 4 hypertriglyceridemia was observed in 20 patients (14.4%) and 5 patients (3.6%) respectively.[7]

In phase II, there were 26 patients (9.5%) and 38 patients (13.8%) that died within 28 days after the last dose of study drug and greater than 28 days after last dose of study drug respectively. Results are displayed in Table 17.

Table 17. Summary of deaths, Phase I and Phase II safety population[3]

Deaths	Phase 1 (N=54) n (%)	Phase 2 (N=275) n (%)	100-mg QD Pooled Group (N=295) n (%)
Patients who died			
Within 28 days after last dose of study drug	7 (13.0)	26 (9.5)	29 (9.8)
More than 28 days after last dose of study drug	20 (37.0)	38 (13.8)	42 (14.2)
Cause of death			
Disease under study	24 (44.4)	59 (21.5)	65 (22.0)
Unknown/not reported	2 (3.7)	1 (0.4)	2 (0.7)
Study treatment toxicity	0	0	0
Other	1 (1.9)[a]	4 (1.5)[b]	4 (1.4)[b]

a. Specified as hypertension, supplemental oxygen dependency, morbid obesity and diabetes (Table 16.2.6.5.2.1).
b. Specified as pneumonia for 2 patients; Probable lung infection and suspected thrombus embolism for 1 patient each (Table 16.2.6.5.2.2).

Treatment-related adverse events due to dose interruptions and dose reductions occurred in 83 patients (30%) and 61 patients (22%) of 275 patients, respectively. Specifically, the most common treatment-related cause for dose interruptions and dose modifications was oedema which occurred in 16 patients (6%) and 18 patients (7%) of 275 patients, respectively. [2]

6.4 Ongoing Trials

Trial Design	Intervention /Experimental Arm	Outcomes
NCT03909971[32] A Phase 2, multi center, open label, dual cohort study to evaluate the efficacy and safety of lorlatinib (PF 06463922) monotherapy in ALK inhibitor treated locally advanced or metastatic ALK positive non small cell lung cancer patients in China Cohort 1: Disease progression after crizotinib as the only ALK inhibitor. Cohort 2: Disease progression after one ALK inhibitor other than crizotinib Actual Study Start Date: April 28, 2019 Estimated Primary Completion Date: August 26, 2020	Intervention: ALK inhibitor-treated ALK-positive NSCL treatment Other Name: PF-06463922 Experimental: Lorlatinib single agent, 100 mg (4 x 25 mg) oral tables, QD, continuously	Primary Outcome: • Objective Response in Cohort 1 Secondary Outcomes: • Objective Response in Cohort 2 • Progression Free Survival • Overall Survival • Intracranial Objective Response • Duration of Response • Duration of Intracranial Response • Time to tumour response • Adverse Event • Laboratory abnormalities

Trial Design	Intervention /Experimental Arm	Outcomes
Estimated Study Completion Date: August 26, 2022		• Vital signs (blood pressure, pulse rate) • 12-Lead Electrocardiograms • Echocardiograms or multigated acquisition scan (MUGA) • Pharmacokinetics (Tmax, AUCt, AUCtau, AUCinf, CL/F,Vz/F, t1/2, Rac) • Body weight
NCT04111705 [33] A Phase II Non-randomized, Single Group Assignment, Open-label, Multicenter Study of Efficacy and Safety of lorlatinib (PF-06463922) Monotherapy After Failure of First-line Second-generation ALK Kinase Inhibitor in Patients With Advanced ALK-positive Non-small Cell Lung cancer Estimated Study Start Date: October 2019 Estimated Primary Completion Date: December 2021 Estimated Study Completion Date: December 2022	Lorlatinib 100 mg once daily (same for Intervention and Experimental)	Primary Outcome: • Objective Response Rate Secondary Outcomes: • Overall Response Rate • Progression Free Survival (PFS) • Disease Control Rate • Duration of Response (DOR) • Time to Tumour Response (TTR) • Central Nervous System (CNS) ORR • CNS PFS • CNS DOR • CNS TTR • Best ORR and PFS

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of lorlatinib in ALK-positive NSCLC:

- Critical appraisal of the sponsor's submitted matching-adjusted indirect comparisons (MAIC) of lorlatinib in second-line or later therapy of ALK-positive NSCLC
- Critical appraisal of a published systematic review and meta-analysis examining the survival of patients with NSCLC without treatment

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

7.1 Summary and critical appraisal of the sponsor-submitted matching-adjusted indirect comparisons (MAIC) of lorlatinib to ceritinib, alectinib, brigatinib, and chemotherapy in patients with ALK-positive NSCLC

7.1.1 Objective

In the absence of data on the comparative efficacy of lorlatinib compared to other available treatments in second-line or later ALK-positive advanced NSCLC, the sponsor undertook an indirect treatment comparison (ITC) in the form of an unanchored matched-adjusted indirect comparison (MAIC) in order to evaluate overall survival and progression-free survival[8] and inform a cost-effectiveness model relevant to the economic evaluation of this report. [9] The objective of this section is to summarize and critically appraise the sponsor-submitted unanchored MAIC comparing lorlatinib with chemotherapy for the treatment of ALK-positive NSCLC. Data from this unanchored MAIC was used in the pharmacoeconomic model comparing lorlatinib with chemotherapy. In the economic model, the assumption was made that the relative efficacy of lorlatinib versus pemetrexed or docetaxel monotherapy is similar to the combination of pemetrexed-platinum. The unanchored MAIC does not include combination of pemetrexed-platinum, rather the economic model assumes relative efficacy of lorlatinib versus pemetrexed or docetaxel monotherapy (from the MAIC) is similar to combination of pemetrexed-platinum. [9]

7.1.2 Findings

Rationale and Objectives

There are multiple treatment options for patients with advanced and/or metastatic ALK-positive NSCLC. The safety and efficacy of one of these treatments, lorlatinib, is currently being investigated in a Phase I/II, single-arm, open-label, non-randomized multicentre clinical trial (NCT01970865). [13]To identify all relevant comparators and assess the safety, efficacy, tolerability, and health-related quality of life (HRQL) of treatment options with this

indication, a systematic literature review (originally conducted by BresMed in 2017) was updated in July 2018. [8]

Source

The MAIC was performed by the sponsor and has not been published or peer reviewed. [8]

Systematic Review

The systematic review, updated in July 2018 (from the original February 2017 search), aimed to assess treatment options for advanced and/or metastatic ALK-positive NSCLC in order to summarize the efficacy, safety, tolerability, and health-related quality of life (HRQL) associated with the treatment options. As this was an updated review, the authors did not describe the specific inclusion/exclusion criteria, but a reference to the statistical analysis plan in which this information is stated, was provided. The literature search yielded a total of 265 articles in the updated review. Relevant data were extracted from 5 RCTs reported in 62 publications and 71 non-RCTs from 203 publications. The reasons for exclusion of studies were not provided. The 5 unique RCTs and 71 non-RCTs were originally grouped by comparator treatment (ceritinib, alectinib, brigatinib, crizotinib, and pemetrexed). A subsequent screening procedure required studies to: 1) include patients already treated with one or more ALK inhibitor and 2) report overall survival (OS) and/or progression-free survival (PFS) Kaplan-Meier (KM) curves. This screening resulted in the identification of 4 relevant comparators: ceritinib, alectinib, brigatinib, and chemotherapy represented by multiple studies which would be pooled by outcome (OS or PFS) in the comparison with the corresponding expansion arm of the patient population in the lorlatinib trial. The current summary and critical appraisal focus solely on the indirect treatment comparison of lorlatinib with chemotherapy. The other comparators were not considered relevant to the review.

For the relevant comparator treatments, 11 studies were identified from the systematic literature review which assessed pemetrexed. The screening procedure led to the identification of two studies with chemotherapy being the relevant comparator and that reported on a relevant outcome (PFS). [34] [35] Reasons for exclusion of the 9 other studies were not provided. Studies were further screened for inclusion into a series of MAICs by assessing the relevance and reliability of each study, which involved assessing the study design, number of patients, and availability of baseline information thought to be a potential prognostic factor or treatment effect modifier. Of note, the data from the lorlatinib trial were obtained solely from the Phase II portion of the trial and limited to the six relevant cohorts (EXP 2, EXP 3, EXP 3a, EXP 3b, EXP 4, and EXP 5), which varied by the extent and type of previous treatment received. [8] Details and relevance of the lorlatinib Phase II trial patient cohorts are outlined in Table 18. No additional details about the index or comparator studies were provided. Further details on the original and updated systematic reviews can be found elsewhere.[8]

Table 18: Lorlatinib Phase II trial patient cohorts and relevance

Study Population	Detail	Relevance to MAIC (to funding request)	N
EXP 2	Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after only crizotinib. No prior chemotherapy was allowed in the metastatic setting	Relevant: 1 prior ALK inhibitor (crizotinib), no prior chemotherapy	27

Study Population	Detail	Relevance to MAIC (to funding request)	N
		(not relevant to funding request)	
EXP 3	EXP 3: Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after crizotinib and 1 or 2 prior regimens of chemotherapy given before or after crizotinib; OR patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting	Relevant: 1 prior ALK inhibitor (crizotinib or other), with or without prior chemotherapy (see below EXP 3a and EXP3b)	60
	EXP 3a: Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after crizotinib and 1 or 2 prior regimens of chemotherapy given before or after crizotinib	Relevant: 1 prior ALK inhibitor (crizotinib or other), with 1 or 2 prior chemotherapy (not relevant to funding request)	32
	EXP 3b: Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor other than crizotinib, with or without any number of prior chemotherapy regimens in any disease setting	Relevant: 1 prior ALK inhibitor (other), with or without chemotherapy (relevant to funding request)	28
EXP 4	Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after 2 prior lines of ALK inhibitors. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting	Relevant: 2 prior ALK inhibitor (crizotinib or other), with or without chemotherapy (relevant to funding request)	65
EXP 5	Patients with advanced ALK+ NSCLC, with or without asymptomatic CNS metastases relapsing after 3 prior lines of ALK inhibitors. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting	Relevant: 3 prior ALK inhibitor (crizotinib or other), with or without chemotherapy (relevant to funding request)	46
Notes: ALK+, anaplastic lymphoma kinase-positive; CNS, central nervous system; EXP – expansion; NSCLC, non-small cell lung cancer			

Methods

Trials included in the MAIC

In order to identify the most appropriate trials to be included in the MAIC, further screening was performed to specifically assess potential prognostic factors and/or treatment effect modifiers to avoid the need to conduct multiple MAICs within each comparator. Potential important prognostic factors were identified in the statistical analysis plan (not provided in the review) and based on the earlier data cut. Further, studies were combined in cases where multiple trials were considered appropriate for each comparator. [8] Details on how the studies were combined were not provided. An exploratory analysis conducted and described in the statistical analysis plan identified the following important prognostic factors in patients with ALK-positive NSCLC: sex, age, race, ECOG performance status, smoking status, brain metastases, and adenocarcinoma. [8] Further exploratory analyses were also conducted using lorlatinib individual patient data (IPD) and by producing Kaplan-Meier (KM) curves for OS and PFS from which it was determined that ECOG PS, race, sex, brain metastases, and body mass index (BMI) were important potential prognostic factors within the lorlatinib trial. Based on clinical feedback and availability of study data, the final factors used to match the comparator studies to lorlatinib were ECOG, age, brain metastases, and race.

Matching Feasibility Assessment

As part of the assessment of feasibility for matching for the indirect comparison, it was deemed more appropriate to match the comparator studies to a subset of the lorlatinib cohorts, which were similar in terms of the line of therapy. [8] This corresponded mainly to cohorts EXP-2 and/or EXP-3a (Table 18). Since age and adenocarcinoma were relatively balanced across the lorlatinib cohorts and comparator evidence, these variables were not used for matching. According to clinical feedback obtained, the most important factors to match to provide comparisons that minimize bias were ECOG, brain metastases, and race.

Outcomes

The main outcomes of interest for the sponsor's MAIC were OS and PFS. No other outcomes were considered in the MAIC.

Methods of Naïve Comparison

A naïve ITC is reported by the Submitter in the MAIC report; however, methodological details were not reported. This information provides a reference case estimate of comparative efficacy between lorlatinib and the relevant comparator, which involves estimating a HR based on median OS and PFS. No adjustments for differences in baseline characteristics between trials are made in this type of ITC.

Methods of MAIC

The comparative efficacy of lorlatinib to chemotherapy was evaluated using both a naïve and a MAIC. These methods used provide an estimate of relative treatment effect that has been adjusted to account for known imbalances in prognostic variables and/or treatment effect modifiers that can be influential on outcome. One difference, however, was that due to the lack of availability of IPD for the identified comparative evidence sources, KM graphs were digitized to create pseudo-IPD using a published algorithm. [36] [37] These pseudo-IPD were considered with the IPD from the Phase II portion of the lorlatinib trial. In cases where there were multiple evidence sources for an outcome (e.g. PFS), pseudo-IPD for the outcome, for

each treatment, was created by digitizing separately and subsequently combining the pseudo-IPD into a single dataset. Corresponding baseline characteristics were then created by calculating weighted averages of the summary statistics . [8]

To make an adjusted comparison between the selected lorlatinib cohorts and the comparative evidence source, individual lorlatinib treated patients were assigned statistical weights that adjust for their over or underrepresentation, relative to that observed in each comparative evidence source. [8] After weighting, average baseline characteristics (mean and variance) were balanced between the selected lorlatinib cohort(s) and the comparative evidence source. [8] Efficacy outcomes for PFS were then compared between balanced treatment groups using statistical tests that incorporated the derived weights and KM curves were generated. Weighted Cox proportional hazards models and 95% confidence intervals (CIs) were then calculated using bootstrapping (to account for within subject correlation induced by the weights) and HRs comparing lorlatinib cohorts and the comparative evidence source were estimated. [8]

Results

The relevant comparator and outcomes are outlined in Table 19. [34] [35]Though not part of the current funding request or economic model, lorlatinib cohorts EXP-2 and EXP-3a were identified by the authors as corresponding most closely to the majority of patient populations in the comparator evidence. For this funding request, the MAIC used individual patient-level data from cohorts EXP3b-5 (February 2, 2018 data cut-off date) for lorlatinib and reweighted these patients to "match" the population of the comparator treatment based on patient/trial characteristics that were identified as treatment effect modifiers or key clinical prognostic factors. Progression-free survival was the only outcome available for the comparison of lorlatinib versus chemotherapy. Both comparator studies assessed pemetrexed or docetaxel and reported the combination treatments as a combined arm. Therefore, a comparison to pemetrexed only was not possible with the available evidence. The two MAICs conducted are outlined in Table 19. It should be noted that this required the assumption that the efficacy of chemotherapy does not differ between the expansion cohort populations.

The final prognostic variables/effect modifiers selected for matching were ECOG PS (categorized as 1, 2, or 0 in the lorlatinib trial), race (Asian, non-Asian), sex (male, female) and brain metastases (yes, no). Since the Novello 2017 study[34] [35]only reported baseline ECOG PS as a 0 or 1/2, this variable was recategorized into a binary variable (i.e., 0 or 1/2). Following the matching procedure, the weighted patient characteristics for lorlatinib were compared with the comparator populations (Table 20). The percentages of lorlatinib patients after matching were the same as the percentages of patients in the comparator populations; the number of patients lost by matching, or the effective sample size, is reported in Table 20.

The results for the MAIC analysis for PFS are presented in Table 21. A significant difference in PFS between lorlatinib and chemotherapy in both cohorts was detected. Lorlatinib being associated with a notably decreased hazard of progression compared with chemotherapy (pemetrexed or docetaxel) is consistent across both the naïve and adjusted comparisons (and compared to the original analysis). Only a very minor difference between the observed and weighted survival curves is reflected by the approximate equivalence of the naïve and adjusted HRs. The treatment difference in the second comparison (using the EXP-5 lorlatinib cohorts) is reduced, but this is to be expected since the health of these patients is

anticipated to be poorer. However, lorlatinib is still shown to significantly reduce the hazard of progression compared with lorlatinib within this population. [8]

Table 19. Corresponding lorlatinib cohorts to the comparator evidence

Comparator	Outcome	Study/studies to be pooled	Corresponding patient population in the lorlatinib trial	Final lorlatinib population matching
Chemotherapy (pemetrexed or docetaxel)	PFS	Novello 2017 Shaw 2017[34] [35]	EXP-3a EXP-3a	EXP-2 and EXP-3a
Chemotherapy (pemetrexed or docetaxel)	PFS	Novello 2017 Shaw 2017[34] [35]	EXP-3a EXP-3a	EXP-3b, EXP-4 and EXP-5
Notes: EXP – expansion, PFS – progression-free survival				

Table 20: Baseline characteristics before and after matching (progression-free survival outcome) [8]

Before/after matching	Treatment comparison	N	ECOG PS 1/2 (%)	Asian (%)	Male (%)	Brain metastases (%)
Before	Lorlatinib population (EXP-2 and EXP-3a)	59	52.54	28.81	33.90	62.71
Before	Lorlatinib population (EXP-3b, EXP-4, and EXP-5)	139	56.12	38.13	43.88	62.59
After	Lorlatinib (EXP-2 and EXP-3a) vs. chemotherapy	56	46.36	29.80	47.68	62.91
After	Lorlatinib population (EXP-3b, EXP-4 and EXP-5) vs. chemotherapy	134	46.36	29.80	47.68	62.91

Table 21: Unadjusted and adjusted hazard ratio results for progression free survival [8]

(updated analyses only)

Comparison	Naïve	Adjusted
	HR (95% CI)	HR (95% CI)
Lorlatinib vs. chemotherapy	0.222 (0.146, 0.336)	0.203 (0.14, 0.288)
Lorlatinib vs. chemotherapy (EXP-3b-5)	0.357 (0.27, 0.472)	0.353 (0.289, 0.43)
Notes: CI, confidence interval; HR, hazard ratio		

Matching-Adjusted Indirect Comparison

Critical Appraisal: Limitations and Sources of Biases

The quality of the sponsor-submitted MAIC was appraised according to best practice principles outlined by Phillippo et al. in the NICE technical support document on methods for population-adjusted indirect comparisons. [38] The pCODR Methods Team observed the following:

- The methods used for systematic literature review that was updated in June 2018 were reasonably well reported. However, there is insufficient evidence that the quality of the individual trials was assessed, which could introduce significant biases in the MAIC analysis. This is a considerable flaw in the methods that may compromise the internal validity of the overall results.

- Given the paucity of evidence in the populations of interest, the lack of comparative trials, and the single-arm trial design of the lorlatinib study, an unanchored MAIC was used to compare treatment outcomes across trial populations. Out of the 11 studies assessing pemetrexed that were originally identified, 9 were excluded but the reasons for exclusion were not provided. While the screening excluded studies that either 1) did not include patients that were already treated with one or more ALK inhibitor or 2) did not report OS and/or PSF KM curves, it is not clear which studies met these exclusion criteria and whether they met one criterion or both. This lack of transparency in how the comparator studies were selected suggests that it may not have been an entirely objective process.

- The methods related to the selection of studies are not transparent. There is subjectivity as to which studies were included and reasons for exclusion of studies were not provided. This is an important critical appraisal point and weakens our confidence in the findings. In MAIC, selection of a comparator trial that is representative of the target population is critical, and with the submitted report, it is unknown if the selected studies reflect this since there is not enough information

about the patient characteristics, background therapies permitted, and standard of care received to determine this.

- Another criticism is that it is difficult to assess whether the studies selected for the MAIC were clinically relevant and whether they are the most representative of the target population (i.e., the population that would be treated in Canada). The selected studies may or may not reflect this and further, there is insufficient information on the patient characteristics, background therapies permitted, etc. to determine this. There also appeared to be no comparison of the inclusion and exclusion criteria of the trials, which is critical to the match of the index and comparator trials.

- The sponsor acknowledges that the MAIC technique introduces some limitations to the analysis. More specifically, the strength of the matching is limited by the number of factors (patient characteristics) that are available in the study being matched, and the factors in the study being matched to. As such, this could mean that important differences in patient characteristics between the studies are not controlled for if sufficient information is not reported. [8] The current MAIC matched four baseline characteristics of the appropriate lorlatinib cohort to the chemotherapy group: ECOG PS 1/2, percentage who were Asian, percentage of males, and the percentage who had brain metastases. According to the NICE document ,[38] *"a major limitation of the unanchored MAIC is that it is susceptible to large amounts of systematic error unless all prognostic variables and effect modifiers are accounted for'"*. It is necessary to attempt to quantify the possible extent of residual systematic error resulting from unobserved or unaccounted for prognostic variables and effect modifiers. They did not appear to do so. According to the NICE document, when this is not done for an unanchored MAIC, "*the amount of bias in the indirect comparison is likely to be substantial and could even exceed the magnitude of treatment effects which are being estimated*".

- Pooled average baseline characteristics from the chemotherapy studies were not reported and as such, it is taken at face value that the weighting resulted in balance.,[38] The approach was largely data-driven (based on data availability) and some factors were excluded (age, adenocarcinoma) because they were balanced prior to weighting on the other factors. However, reweighting could lead to imbalance on the factors that they chose not to adjust for (e.g., age). It is therefore critical to consider whether there are other clinical characteristics that might be essential for comparison, such as disease stage, or histology, which left unmatched, could be significant effect modifiers.

- In the current MAIC, effective sample sizes were reduced from 59 to 56 after matching and weighting for the lorlatinib EXP2-3a comparison and from 139 to 134 after matching and weighting for the lorlatinib EXP 3b-5 comparison. The authors acknowledged that the MAIC process leads to a reduction in 'effective' sample size, which can lead to higher variability in the results and larger confidence intervals. However, this was not the case in the current study.

- While PFS for the lorlatinib trial was defined, it was not reported whether the two comparative studies used the same definition. Further, ECOG PS was reported in the lorlatinib trial as a 0, 1, or 2 but in one of the matched studies was reported as a

binary variable (0, 1/2), which required summarizing the ECOG PS data into a similar binary variable. These differences between trials, while small, are not ideal.

- Comparative evidence on pemetrexed for OS was not available. Further, the authors note that the available evidence does not specifically target pemetrexed, which is the key comparator of interest for the MAIC analyses. Rather chemotherapy, which also included docetaxel, was assumed to appropriately represent survival for pemetrexed.

- The authors also caution that relative treatment effects following the MAIC were estimated using HRs as the summary statistic, which may not be appropriate in cases where there is a violation in proportional hazards. However, based on the reported KM survival curves for observed and MAIC adjusted lorlatinib versus chemotherapy, this did not appear to be the case and the presentation of HRs is appropriate. Other relevant outcomes, such as safety and quality of life, were not considered.

- MAIC cannot adjust for any differences or heterogeneity related to design (methodology). The lorlatinib study was a single arm clinical trial. But how this compares to the comparator studies, whether there was any additional care received, details about follow-up and cointerventions were not reported.

Summary

Using unanchored MAIC, the relative efficacy of lorlatinib was compared to chemotherapy for the outcome of PFS and this outcome was used in the economic evaluation of the current report. The cohorts from the lorlatinib trial that were relevant to this funding request were EXP 3b-5. For both lorlatinib cohorts, a significant decrease in hazard ratio compared with chemotherapy (pemetrexed or docetaxel) for the outcome of PFS was detected using unanchored MAIC. The results may be biased due to unmeasured baseline characteristics and failure to conduct a quality assessment of the included studies. Further, it is unlikely that all important effect modifiers and prognostic factors were included due to the lack of data. Residual error was also not assessed and therefore, the overall results should be interpreted with caution. Due to the availability of data, no comparison to chemotherapy for the outcome of OS was conducted.

7.2 Summary and critical appraisal of a published systematic review and meta-analysis examining the survival of patients with NSCLC without treatment

7.2.1 Objective

The objective in this section is to summarize and critically appraise the published systematic review and meta-analysis by Wao et al. [10] in which overall survival is estimated in lung cancer patients when no anticancer therapy is provided. The CGP identified BSC as a relevant comparator. In the absence of a head to head trial comparing lorlatinib to BSC and

due to the limited ability to conduct an ITC, the sponsor proposed to match survival outcomes to those reported in this published systematic review.

7.2.2 Findings

Objectives of published systematic review and meta-analysis

Decisions related to the management of lung cancer require accurate prognosis of the disease with *or* without treatment. Since systematic assessment of the prognosis in patients with lung cancer without treatment had not been performed, Wao et al. [10]sought to estimate overall survival in this patient population by conducting a systematic review and meta-analysis in order to assist clinicians in making evidence-based recommendations for management decisions related to this disease.

Methods

A systematic review aimed at estimating overall survival in lung cancer patients when no active therapy is provided was conducted by Wao et al. in 2013. The authors stated that the systematic review was conducted according to the methods described in a protocol that was developed a priori, however, these methods are not described in the paper nor is a reference to these methods provided. Wao et al. described that an inception cohort study is the ideal study design to assess the natural history of a terminal disease however, given the availability of treatments for lung cancer in recent years, it would be unethical and logistically challenging to conduct an inception cohort study. Therefore, Wao et al. proposed an alternate approach (i.e. assess prognosis from retrospective lung cancer registries, case series or from the control arm of individual RCTs that compare active treatment with either no treatment, placebo, or best supportive care). In an attempt to illustrate the patient population, intervention, comparator and outcome (PICO), the Methods Team created Table 22:

Table 22: Study design, patient population, intervention, comparator and outcome

Study Design	Patient Population	Intervention	Comparators	Outcome
retrospective lung cancer registries, case series or randomized controlled trials*	lung cancer patients	no active therapy/no treatment (e.g., placebo, best supportive care, palliative care)	N/A	Overall Survival

*randomized controlled trials from the control arm of individual RCTs that compare active treatment with either no treatment, placebo, or best supportive care
N/A = not applicable

Search terms were provided, and the search included retrospective or prospective cohort studies assessing prognosis in lung cancer without treatment, and any RCT comparing treatment versus no treatment, placebo, or best supportive care.

Studies had to assess overall survival as an outcome for inclusion. Eligible studies published until June 2011 obtained via systematic search of MEDLINE, the Cochrane library, conference proceedings, bibliographies of eligible studies, and a manual search of conference abstracts were included. There were no restrictions on language or publication type. Appropriate MeSH terms were used to optimize the sensitivity and specificity of the search. Studies in which patients had anticancer treatment prior to enrollment, subgroup analyses, and RCTs comparing two active treatments were excluded. Study selection and data extraction were performed independently and in duplicate and disagreements were resolved via consensus.

While data extraction was performed by two independent reviewers, it is not clear whether the methodological quality of the included studies was assessed in duplicate. A checklist was developed that modified existing published quality assessment tools (e.g. Newcastle-Ottawa Quality Assessment Scale, Cochrane Collaboration risk of bias criteria) to create four methodological domains relevant to the minimization of bias. The modified list contained 11 criteria for cohort studies and 14 criteria for RCTs. The probability of bias for each domain was assessed as a binary outcome based on whether a study fulfilled a particular criterion (yes/no). The biases assessed were participation bias (extent to which study sample represents the population of interest on key characteristics), attrition bias (extent to which loss to follow up of the sample was not associated with key characteristics), outcome measurement bias (extent to which outcome of interest is adequately measured in study participants), and reporting bias (extent to which statistical analysis and data reporting are appropriate for the study design). The reliability and validity of this modified quality assessment tool was not evaluated. While the number and proportion of studies that fulfilled each criterion was reported, these data were only reported in aggregate form, and references to the individual studies meeting (or not meeting) each criterion were not reported. Importantly, sensitivity analyses with and without the lesser quality studies would have been useful but difficult given that the new instrument had not been validated. The criteria used to assess the methodological quality of the included studies are outlined in Table 23.

Data were synthesized separately according to the study design (retrospective cohort versus RCT) and then subsequently combined. The authors refer to methods described by Stuart et al. for the meta-analysis and briefly explain that "the proportions were transformed into a quantity according to the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as a back-transform of the weighted mean of the transformed proportions using the random-effects model". The rationale for using the random-effects model was not provided. To perform meta-analysis of median survival, published methods [39]were used to pool the estimates as mean survival and standard error under the random-effects model. In other words, median survival and range, as reported in the Kaplan-Meier curve, were further converted into mean survival and standard error. Of note, it is unclear if the survival data from the RCTs were mature, as no details on the maturity of data were report nor were methods for dealing with immature data in the analysis were described. Heterogeneity of treatment effects between trials was assessed using the I-squared statistic using thresholds defined as low (25-49%), moderate (50-74%), and high (≥75%). Potential causes of heterogeneity were assessed by examining the differences between subgroups using the test of interaction. Finally, a sensitivity analysis

incorporating the methodological quality criteria of reporting, study location, and funding source was conducted to test the robustness of results.

Table 23: Methodological quality domains and criteria of lung cancer prognosis studies

Domain/Criterion
Participation Bias
Population of interest is adequately described for key characteristics
Study setting and geographic location is adequately described
Baseline sample is adequately described for key characteristics
Inclusion and exclusion criteria are adequately described
There is adequate participation in the study by all eligible patients (Cohort studies only)
Patients were balanced in all aspects except the intervention (RCTs only)
Attrition Bias
Follow-up is sufficiently long for outcome to occur (≥6 months)
Patients with missing data were reported (Cohort studies only)
Proportion of sample completing the study is adequate (≥80%) (RCTs only)
Description of withdrawal (incomplete outcome date) is provided (RCTs only)
Characteristics of drop-outs versus completers is provided (RCTs only)
Outcome Measurement
Definition of outcome is provided a priori
Objective definition of outcome is provided
Data Analysis and Reporting
Alpha error and/or beta error is specified a priori
Frequencies of most important data (e.g. outcomes) are presented
Data analysis was based on intention-to-treat analysis principle (RCTs only)

Results

The results reported by Wao et al. were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The selection criteria for all included and excluded studies were well outlined in a flow diagram and described. Twenty-two studies, 7 retrospective cohort studies and 15 RCTs, met the pre-defined inclusion criteria. Descriptions of the various quality criteria (based on their unvalidated assessment tool) were generally well-reported in both the cohort studies and RCTs with the exception of alpha and/or beta error being specified a priori, which were only reported in 29% and 47% of the studies, respectively. Among the RCTs, the characteristics of the drop-outs versus completers was only described in 2 out of 15 trials (13%) and follow-up was sufficiently long for the outcome to occur in 53% of the trials. Further, data analysis was based on the intention-to-treat principle in 53% of the RCTs.

A total of 5,449 patients were included in the 22 studies (4,418 patients from the 7 retrospective cohort studies and 1,031 patients from the 15 RCTs). When available, the following characteristics of the cohort studies and RCTs included in the review were reported: sample size, study period (years), disease stage (I-IV), histology (adenocarcinoma, squamous cell, or large-cell), gender, and median age. The median sample size in the cohort studies was 131 patients (range: 39 to 2,344 patients) with a median study duration of 8 years (range: 5 to 13 years). The median sample size in the RCTs was 61 patients (range: 17 to 176) with a median study duration of 3 years (range: 1 to 7 years). Median follow up was reported in 33% (5/15 of RCTs) and ranged between 2.7 and 43 months. Among the cohort studies, 57% (4/7) and 29% (2/7) reported the number of patients with stage I and stage II NSCLC, respectively. Forty-three percent (3/7) reported patients' cancer histology,

71% of the studies reported patient's gender, and 43% (3/7) of the cohort studies reported median age. Among the RCTs, 73% (11/15) reported the number of patients with stage III/IV NSCLC. Eighty-seven percent (13/15) reported patients' cancer histology and 87% (13/15) of the RCTs reported patients' gender and median age. Among the cohort studies, 43% (3/7) were conducted at single institutions, 43% (3/7) at multicenter national institutions, and 14% (1/7) did not specify study location. Twenty-nine percent (2/7) of the cohort studies were publicly funded, 14% (1/7) were funded by both public and industry, and 57% (4/7) did not specify their source of funding. Among the RCTs, 20% (3/15) were conducted at single institutions, 27% (4/15) were multicenter national studies, 20% (4/15) were multicenter international studies, and 33% (5/15) did not specify study location. Seven percent (1/15) of the RCTs were publicly funded, 33% (5/15) by industry, 7% (1/15) by both the public and industry, and 53% (8/15) did not specify their source of funding.

With respect to the types of control in the RCTs, there was some variability between studies in their descriptions of *best supportive care* (also referred to as supportive care, palliative care, symptomatic treatment). Treatments included under the umbrella of best supportive care included palliative radiotherapy, symptomatic or palliative treatment excluding chemotherapy, antibiotics, corticosteroids, opioid analgesics, psychosocial support, nutritional support, thoracocentesis and/or tube thoracoscopy, antitussives, relief of increased cranial pressure, treatment of infections and pleural effusions, symptomatic irradiation to involve fields, glucocorticosteroids and anabolic steroids. Descriptions of *placebo* and *no treatment* were not provided in any of the included studies.

Mortality Outcome

All 4,418 patients from the 7 cohort studies were included in the pooled analysis for mortality. The pooled proportion of mortality without treatment in cohort studies was 0.97 (95% CI, 0.96 to 0.99). There was statistically significant heterogeneity between studies (I-squared=93%, p<0.00001).

All 1,031 patients from the 15 RCTs were included in the pooled analysis for mortality. The pooled proportion of mortality in the control (no active treatment) arm in the RCTs was 0.96 (95% CI, 0.94 to 0.98). Statistically significant heterogeneity between studies was detected (I-squared=80%, p<0.00001).

When the data from the cohort studies and RCTs were combined, the pooled proportion of mortality across the 22 studies was 0.97 (95%CI, 0.96 to 0.98). When tested for subgroup differences, Wao et al. report that no statistically significant heterogeneity between the study designs (cohort versus RCT) was reported (p=0.28).

Median Survival Outcome

The data on median overall survival was extractable from 6 cohort studies (4,125 patients). The pooled *mean* survival was 11.94 months (95% CI, 10.07 to 13.8). Statistically significant heterogeneity among the pooled cohort studies was detected (I-squared=97%, p<0.00001).

The data on median overall survival came from all 15 RCTs (1,031 patients). The pooled mean survival for patients in the untreated arm was 5.03 months (95% CI, 4.17 to 5.89). Statistically significant heterogeneity among the pooled RCTs was detected (I-squared=90%, p<0.00001).

When the data from the cohort studies and RCTs were combined, the pooled proportion of mortality across the 21 studies was 7.15 months (95% CI, 5.87 to 8.42). When tested for

subgroup differences, statistically significant heterogeneity between study designs was detected (I^2=97.7%, P <0.00001).

Sensitivity Analysis

A sensitivity analysis was conducted to explore the reasons for the observed heterogeneity in the pooled proportion of mortality and mean survival and to assess the robustness of the overall results. Sensitivity analyses were conducted for both study designs according to methodological quality criteria, funding source, and study location, and type of control (for RCTs only) though it is not clear whether these analyses were planned a priori. Overall, the results remained unchanged and no significant differences in the proportion of mortality were detected.

When examined individually, there were no statistically significant differences in the proportion of mortality in the *cohort studies* according to methodological criteria. The pooled proportion of mortality in cohort studies according to study location did vary with a proportion of 0.95 (95% CI, 0.89 to 1.01) at multicenter national locations, 0.98 (95% CI, 0.95 to 1.01) at single institutions, and 0.87 (95% CI, 0.82 to 0.93) at unspecified locations. The test for overall interaction among these subgroups was statistically significant (p=0.007). There was also a statistically significant (p<0.0001) overall interaction among the funding source subgroups with the pooled proportion of mortality in public-funded, unspecified funding sources, and combination public and industry-funded cohort studies of 1.00 (95% CI, 1.00 to 1.00), 1.00 (95% CI, 0.99 to 1.00), and 0.97 (95% CI, 0.96 to 0.98), respectively.

There were no statistically significant differences in the proportion of mortality in the *RCTs* according to methodological criteria, study location, or funding source. With respect to types of control, these were categorized for the pooled analysis as best supportive care, no treatment, placebo, supportive care, and symptomatic treatment. The pooled proportion of mortality in RCTs involving best supportive care, no treatment, placebo, supportive care, and symptomatic treatment as control was 0.90 (95% CI, 0.83 to 0.97). In RCTs involving supportive care as control the pooled proportion was 0.96 (95% CI, 0.92 to 1.00), 0.86 (95% CI, 0.81 to 0.92), 1.00 (95% CI, 0.99 to 1.01), 0.96 (95% CI 0.92 to 1.00), and 0.97 (95% CI, 0.92 to1.03), respectively. A statistically significant interaction among these subgroups was detected (p<0.00001).

Performing a subgroup analysis based on median follow up was considered, however, only one cohort study and 5 RCTs reported these data. The median follow-up in the cohort study was 40 months and in the RCTs, the median follow up was 2.7, 13, 26, 40, and 40 months, respectively.

Critical Appraisal: Limitations and Sources of Biases

The quality of the systematic review and meta-analysis conducted by Wao et al. was appraised according to the AMSTAR 2 critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. [40] The pCODR Methods Team noted the following:

- This systematic review and meta-analysis were published in 2013 and the literature review included studies published until June 2011. There may be additional studies published between 2011-2019 that could be added to conduct an updated analysis of mortality in untreated patients with NSCLC.

- The research question and inclusion criteria for the review included the components of PICO and the authors reported that the review methods were established a priori.

The results were reported according to PRISMA. Study selection and rationale for inclusion/exclusion of studies were clearly reported. A comprehensive literature search was conducted, however, there was no indication that grey literature or experts in the field were consulted in order to identify relevant studies. It was also not reported whether trial or study registries were searched. Study selection and data extraction were appropriately performed in duplicate. Included studies were well described in adequate detail (described PICO, research designs, study setting, and timeframe for follow-up) and source of funding for the included studies was also well reported. As with the primary studies, Wao et al. also reported their funding sources and that there were no conflicts of interest.

- There were weaknesses in the reporting of some measures outlined in the AMSTAR 2 tool. While the authors did assess the risk of *some* measures of bias in individual studies, the assessment was not exhaustive. Rather, Wao et al. focused on four domains (participation bias, attrition bias, outcome measurement bias, data reporting bias) and reported in binary form whether or not individual studies met the criteria for risk of bias (RoB) for each domain. An important criticism in their quality assessment is that a modified tool, albeit whose domains were created using existing reliable and valid quality assessment tools, was used and the reliability and validity of the modified tool had not been tested.

- The pooled proportion of mortality in the cohort studies varied according to study location. However, this result is not particularly informative given the authors' inclusion of studies that did not specify a location (and categorization as 'unknown' in the pooled analysis). This is a limitation to interpretation when these studies could have been excluded from the subgroup analysis. The 'unspecified' category with respect to funding source presents a similar limitation.

- There was no statement on whether publication bias was assessed despite the existence of tools that can assess this. This is important particularly since pooled analyses were conducted. The exclusion of studies may be due to low methodological quality, which can lead to erroneous results.

  An additional limitation in the reporting of the methodological quality of the cohort studies and RCT included in the systematic review pertains to how the quality criteria were presented. For each criterion outlined in Table 23, the number of studies that met or did not meet that criterion were presented in aggregate form and no references to the individual studies were provided. As such, one is unable to determine which studies are of lesser quality and consider the impact of including or excluding them from the meta-analyses. This is an important weakness in the overall review.

  It is also not clear whether there was an adequate assessment of selection biases, bias in measuring exposures and outcomes, and selective reporting of analyses or outcomes, or both, in the randomized and cohort studies. Further, biases due to missing data did not appear to be an important consideration, since those studies that had clinically relevant missing data (eg. disease stage, histology, median age) were still included in the meta-analysis. This is of concern in the cohort studies since the study that was most heavily weighted in terms of sample size (n=2,344 out of a total of 4,418 total for cohort studies) had the most missing baseline data. This is also problematic with missing data on outcomes. The study with the second largest sample size (n=1,432) was also missing data on disease stage, which means the studies that account for 85% of the sample size were missing data on disease

stage and/or histology but were still included in the pooled analysis. Not only can the inclusion of studies with large amounts of missing data have an impact on the meta-analysis results, the effective estimates in the individual study with large amounts of missing data can also be compromised. It is difficult to know with certainty how the effective estimate is biased (whether in favour or not) without proper sensitivity analysis to account for missing data.

- The appropriateness of pooling the cohort studies with the RCTs is highly questionable. First, among the cohort studies, 57% (4/7) and 29% (2/7) of the studies reported the number of patients with stage I and stage II NSCLC, respectively. Seventy-three percent (11/15) of the RCTs reported the number of patients with stage III/IV NSCLC. Differences between the study designs with respect to study duration, histology, gender, age, and type of institution in which the study took place are additional contributors to the observed heterogeneity. Further, the assessment of other methodological considerations such as background care and previous treatments, which are generally more strictly controlled in RCTs, was limited. Statistically significant heterogeneity was detected for the mortality outcome among the pooled cohort studies and the pooled RCTs. The large discrepancy in pooled mean survival for the cohort and RCTs (11.94 months versus 5.03 months, respectively) further suggests that pooling across study designs may be inappropriate. However, when the studies from the two designs were combined and tested for subgroup differences (methodological quality criteria, funding source, and study location), no statistically significant heterogeneity was detected. Reasons for the observed heterogeneity were explored but could not be explained through subgroup analyses. Yet, pooling across study designs was still performed and the authors attributed the observed heterogeneity to clinical, not methodological factors.

- A thorough assessment and explanation of clinical heterogeneity was not provided, although it appears that significant clinical heterogeneity did exist.

- The meta-analysis included all NSCLC patients, whereas the population of interest in this pCODR review is ALK positive patients.

- In the meta-analysis, there were 15 RCTs in which patients did not receive previous anticancer treatment prior to enrollment (i.e. newly diagnosed, first-line patients) which is a different population of interest in this pCODR review.

- A total of 14 studies were conducted between the 1970s and the year 2000 as the authors noted that the availability of various treatments in first-line made it unpractical and unethical to obtain similar results in the modern era. As a result, it is plausible that the results reported by Wao et al. may overestimate OS compared to a theoretical cohort of patient having received multiple lines of previous systemic therapy

7.2.3 Summary

Survival of patients with NSCLC who were not receiving treatment was assessed in a systematic review and meta-analysis published in 2013. The meta-analysis of seven cohort studies and 15 RCTs concluded that the pooled proportion of mortality without treatment in cohort studies was 0.97 and 0.96 in RCTs over median study periods of eight and three years, respectively. When data from all 22 studies were combined, the pooled proportion of mortality was 0.97. No significant difference between subgroups by study design was detected. The pooled mean survival

for patients without treatment in the cohort studies was 11.94 months (95% CI, 10.07 to 13.8), 5.03 months (95% CI, 4.17 to 5.89) in the RCTs, and 7.15 months (95% CI, 5.87 to 8.42), with a statistically significant difference between designs. Several weaknesses of the review are outlined in the current appraisal. These limitations, combined with the flaw in the presentation of the methodological quality of the included studies, limits the overall confidence in the results of this review and as such, the prognosis of patients with NSCLC without treatment is uncertain.

8 COMPARISON WITH OTHER LITERATURE

The sponsor provided real world evidence (RWE) as supportive evidence. Based on consultation with members of the CGP, selection criteria for the review were developed and outlined in the protocol (see Section 6.2.1). Thus, these RWE studies did not meet the a priori study design criteria outlined in Section 6: Systematic Review.

The French nominative Temporary Authorization of Use (nATU) is a non-randomized observational study that included 336 patients treated with lorlatinib across 140 centers. The study involved no formal protocol, statistical analysis plan, data monitoring, or case report form were in place for collection or analysis of these data.[7]

Similarly, a non randomized study was conducted at a single institution in Austria that included 32 NSCLC patients previously treated with various chemotherapies and TKIs that received with lorlatinib (100mg daily p.o.) in an pre-approval access program between June 2016 and April 2019.[11] Due to the small sample size and study conducted at a single site, this limits the external validity of the results to the broader target population.

In Turkey, a single-arm, open-label, multicenter early access program was available across 27 oncology centres between February 2017 and December 2018. Ninety-one patients received treatment with lorlatinib (100 mg p.o/day) if they had advanced stage *ALK*- or *ROS1*-positive NSCLC and had progressed on crizotinib and/or second generation ALK inhibitors such as ceritinib or alectinib.[12] As the study was open-label, investigators and patients were not blinded to the treatment patients received which may impact the internal validity of the results.

Based on the aforementioned methodological limitations, the evidence from these RWE studies are not robust. Therefore, conclusions on the safety and efficacy of lorlatinib cannot be made.

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 lorlatinib for 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** May 2019**, Embase** 1974 to 2019 June 20**, Ovid MEDLINE(R) ALL** 1946 to June 20, 2019

#	Searches	Results
1	(Lorbrena* or lorlatinib* or Loratinib* Lorviqua* or PF06463922 or PF-06463922 or PF6463922 or PF-6463922 or OSP71S83EU).ti,ab,ot,kf,kw,hw,nm,rn.	562
2	1 use medall	110
3	1 use cctr	19
4	2 or 3	129
5	*lorlatinib/	77
6	(Lorbrena* or lorlatinib* or Loratinib* Lorviqua* or PF06463922 or PF-06463922 or PF6463922 or PF-6463922).ti,ab,kw,dq.	349
7	5 or 6	350
8	7 use oemezd	225
9	8 not (conference review or conference abstract).pt.	143
10	4 or 9	272
11	remove duplicates from 10	165
12	8 and (conference review or conference abstract).pt.	82
13	limit 12 to yr="2014 -Current"	79

14	11 or 13	244
15	limit 14 to english language	236

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#3	Search #1 AND #2	5
#2	Search publisher[sb]	469150
#1	Search 7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo(4,3-h)(2,5,11)benzoxadiazacyclotetradecine-3-carbonitrile [Supplementary Concept] OR Lorbrena*[tiab] OR lorlatinib*[tiab] OR Lorviqua*[tiab] OR Loratinib*[tiab] OR PF06463922[tiab] OR PF-06463922[tiab] OR PF6463922[tiab] OR PF-6463922[tiab] OR OSP71S83EU[rn]	111

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

http://www.canadiancancertrials.ca/

Search: Lorbrena/lorlatinib, non-small cell lung cancer

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)

https://www.ema.europa.eu/

Search: Lorbrena/lorlatinib, non-small cell lung cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)

https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

Search: Lorbrena/lorlatinib, non-small cell lung cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[41]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 Lorbrena/lorlatiniband.

No filters were applied to limit the retrieval by study type. 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 October 24, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[42] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's 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 CADTH Clinical Guidance Panel. As well, 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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