CADTH

CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

BRIGATINIB (ALUNBRIG)

(Takeda Canada Inc.)

Indication: For the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor.

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Abbreviations

AE	adverse event
ALK	anaplastic lymphoma kinase
AST	aspartate aminotransferase
BID	twice a day
BIRC	blinded independent review committee
CCO	Cancer Care Ontario
CGP	CADTH Clinical Guidance Panel
CI	confidence interval
CNS	central nervous system
CR	complete response
CrI	credible interval
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ESS	effective sample size
GHS/QOL	global health status quality of life
HR	hazard ratio
HRQoL	health related quality of life
IASLC	International Association for the Study of Lung Cancer
IFCT	French Cooperative Thoracic Intergroup
INV	investigator assessment
iORR	intracranial objective response rate
IPCW	inverse probability of censoring weights
IPD	individual patient data
iPFS	intracranial progression-free survival
ITC	indirect treatment comparison
KM	Kaplan-Meier

LCC	lung cancer Canada
LS	least square
MAIC	matched adjusted indirect treatment comparison
MSM	marginal structural model
NR	not reached
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	objective response rate
OS	overall survival
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PR	partial response
QD	once a day
QLQ	Quality of Life Questionnaire
QoL	quality of life
RCT	randomized controlled trial
RPSFTM	rank preserving structural failure time model
TKI	tyrosine kinase inhibitor
TTR	time to response

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 brigatinib for non-small cell lung cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of brigatinib (Alunbrig) as monotherapy compared with crizotinib for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC.

Brigatinib is an oral tyrosine kinase receptor inhibitor and antineoplastic agent which acts as both an ALK and epidermal growth factor receptor (EGFR) inhibitor. Brigatinib as monotherapy has been issued marketing authorization without conditions for the first line treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC. Brigatinib has the following CADTH reimbursement criteria: For the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor. Note that the Health Canada indication differs from the reimbursement criteria, in that it specifies ‘for the first line treatment’ in its indication and omits ‘previously untreated with an ALK inhibitor’.

The recommended dose of brigatinib is 90 mg administered orally once daily (with or without food) for the first seven days. If tolerated the dose is increased to 180 mg administer orally once daily. Brigatinib should be continued until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the ALTA-1L trial (N = 275). A summary of the trial and its results is provided below.

ALTA-1L

The ALTA-1L trial is an ongoing, open-label, international, multi-centre, active-controlled, randomized phase III trial of brigatinib compared to crizotinib in patients with advanced ALK-positive NSCLC who had not previously received an ALK inhibitor.[1] Patients were randomized in a 1:1 ratio to receive either brigatinib or crizotinib. Randomization was stratified according to the presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease.

Patients randomized to brigatinib received a 90 mg oral dose once daily for 7 days, then 180 mg orally once daily continuously. Patients randomized to crizotinib received an oral 250 mg dose twice daily. Patients continued study treatments until they experienced disease progression, unacceptable toxicity, or were discontinued for other reasons (discontinuation criteria included: entry into another clinical study, start of a new anticancer therapy, significant deviation from the protocol or eligibility criteria, non-compliance with study procedures, pregnancy). After experiencing progressive disease, participants in the brigatinib group could

continue the study treatment if they continued to experience clinical benefit in the opinion of the investigator, and patients in the crizotinib group could crossover from crizotinib to brigatinib at the investigator's discretion.[1,2]

To be eligible, patients needed to be adults with stage IIIB/IV ALK-positive NSCLC, at least one measurable lesion according to RECIST version 1.1 criteria, previously untreated with an ALK inhibitor, received ≤ 1 systemic chemotherapy regimen, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Brain metastases at baseline were allowed if they were asymptomatic. Patients who had previous treatment with an investigational anticancer agent, a tyrosine kinase inhibitor (TKI), or more than one regimen of systemic anticancer therapy were excluded.

The primary endpoint of the trial was blinded independent review committee (BIRC)-assessed progression-free survival (PFS), defined as the time from the day of randomization until the day of disease progression or death from any cause, whichever occurred first. Disease progression was assessed by the BIRC according to RECIST version 1.1 criteria. Key secondary outcomes were confirmed objective response rate (ORR) by BIRC, intracranial ORR by BIRC, intracranial PFS by BIRC, and overall survival (OS). Additional secondary outcomes included duration of response (DOR), change from baseline scores in global health status (GHS)/quality of life (QOL) assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3.0), time-to-deterioration in dyspnea assessed with the EORTC lung cancer-specific module (QLQ-LC13, version 3.0)[1], and safety and tolerability. The EORTC QLQ-LC13 was added as protocol amendment, and only patients enrolled after the protocol amendment were included in the analysis of time-to-deterioration in dyspnea.

A total of 275 patients were randomized in the ALTA-1L trial, with 137 allocated to brigatinib and 138 allocated to crizotinib.[1] Overall, the distributions of baseline characteristics between the treatment groups were well-balanced. The median age of patients was 59 years old, with a range of 27 to 89 years. Most patients were female (55%), of non-Asian race (61%), never smoked (58%), and had an ECOG status of 0 or 1 (96%). Most of the non-Asian patients were White (97%). Most patients had metastatic disease (93%) and adenocarcinoma histological type (96%). Overall, 27% of patients had received previous chemotherapy and 27% of patients had prior radiation therapy.[1,3] Brain metastases were present in 29% of patients at baseline as assessed by the investigator.

Two interim analyses were planned for after approximately 50% (N = 99) and 75% (N = 149) of expected PFS events (disease progression or death) occurred. The overall two-sided type I error for the primary outcome (PFS by BIRC) was controlled at 0.05 using an O'Brien-Fleming Lan-DeMets alpha spending function. The final analysis for the primary outcome was planned to be performed after 198 events are observed, and BIRC-assessed. For the key secondary outcomes (confirmed ORR by BIRC, intracranial ORR by BIRC, intracranial PFS by BIRC, and overall survival [OS]), the overall type I error rate was controlled at 0.05 using a closed testing procedure.

Efficacy

The results for the primary and secondary efficacy outcomes from the ALTA-1L trial are summarized in Table 1. At the first interim analysis (February 19, 2018 data cut-off), median follow-up times for patients in the brigatinib and crizotinib groups were 11.0 months and 9.3 months, respectively. At the second interim analysis (July 28, 2019 data cut-off), median follow-up times for patients in the brigatinib and crizotinib groups were 24.9 months and 15.2 months, respectively. The trial is still ongoing for patient follow-up and the final analysis is expected to be completed in June 2021 as a landmark analysis.

As of the first interim analysis, the ALTA-1L trial met its primary endpoint by demonstrating statistically significant improvement in BIRC-assessed PFS with brigatinib compared to crizotinib (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.33 – 0.74; $P < 0.001$).[1] In the intention-to-treat (ITT) population, the median BIRC-assessed PFS was not reached (NR) in the brigatinib group versus 9.8 months (95% CI, 9.0 – 12.9 months) in the crizotinib group.[1] The estimated 12-month PFS rate was 69% (95% CI, 59 – 76%) in the brigatinib group compared to 40% (95% CI, 30 – 50%) in the crizotinib group (HR, 0.45; 95% CI, 0.30 – 0.68).

The PFS results at the second interim analysis were consistent with those at the first interim analysis. Since the primary endpoint was met at the first interim analysis, subsequent analyses of BIRC-assessed PFS are considered non-inferential. The median BIRC-assessed PFS was 24.0 months (95% CI, 18.5 – NR) in the brigatinib group versus 11.0 months (95% CI, 9.2 – 12.9 months) with crizotinib.[2] Consistent with the first interim analysis, brigatinib was associated with an improvement in PFS as compared to crizotinib

(HR, 0.49; 95% CI, 0.35 – 0.68; *P* < 0.0001).[2] The estimated 24-month BIRC-assessed PFS rate was 48% (95% CI, 39 – 57%) in the brigatinib group versus 26% (95% CI, 18 – 35) in the crizotinib group.[2]

As of the second interim analysis, OS data were immature based on a total of 70 deaths (25% maturity).[2] In the ITT population, 33 (24%) patients in the brigatinib group and 37 (27%) patients in the crizotinib group had died. The median OS was not reached in either treatment group. The results of the other key secondary outcomes assessed (confirmed ORR by BIRC, intracranial ORR by BIRC, intracranial PFS by BIRC) favoured brigatinib as of the second interim analysis (Table 1).

As of the second interim analysis, brigatinib delayed median time to worsening of GHS/QoL scores from the EORTC QLQ-C30 compared to crizotinib. The median time to worsening of GHS/QoL score by ≥ 10 points was 26.7 months (95% CI, 8.3 months – NR) and 8.3 months (95% CI, 5.7 – 13.5 months) in the brigatinib and crizotinib groups, respectively (HR, 0.70; 95% CI, 0.49 – 1.00; P = 0.049). A total of 141 (51%) patients were included in the EORTC QLQ-LC13 analysis. Of this subset of patients, 22% in the brigatinib group and 33% in the crizotinib group experienced worsening dyspnea, defined as a 50% decline from baseline (HR, 0.54; 95% CI, 0.28 – 1.04; *P* = 0.0658).

Harms

Harms outcomes in the ALTA-1L trial as of the second interim analysis are summarized in Table 1. The type of and frequency of adverse events (AEs) were similar at both data cut-offs. The number of patients that experienced an any-grade AE was similar in both treatment groups. Overall, 99.6% of patients in the treated population experienced an any-grade AE as of the second interim analysis. The most frequently reported any-grade AEs (brigatinib vs. crizotinib) were diarrhea (52% vs. 56%), nausea (30% vs. 58%), and increased blood creatine phosphokinase (46% vs. 17%).

As of the second interim analysis, a greater proportion of patients in the brigatinib group experienced a ≥ grade 3 AE compared to the crizotinib group (73% vs. 61%, respectively). The most commonly reported ≥ grade 3 AEs in the brigatinib group were increased blood creatine phosphokinase (24%), increased lipase (14%), and hypertension (12%). In the crizotinib group, the most commonly reported ≥ grade 3 AEs were increased alanine aminotransferase (ALT) (10%), increased aspartate aminotransferase (AST) (7%), and increase lipase (7%). There were more events of interstitial lung disease and pneumonitis (early onset and late onset) in the brigatinib group (n = 4, 3%) than in the crizotinib group (n = 1, 1%). Early onset interstitial lung disease/pneumonitis occurred in 5 brigatinib-treated patients: 4 patients (2.9%, 4/136) from the brigatinib group in the randomized phase, and 1 patient (1.6%, 1/61) from the crizotinib group in the crossover phase.

Limitations and Potential Sources of Bias

The major limitations and potential sources of bias associated with the ALTA-1L trial, based on the CADTH Methods Team's critical appraisal of the evidence, are summarized below. The complete list is available in section 6.

- Based on the guidance from the clinical experts consulted by CADTH, alectinib is the ALK inhibitor of choice in the first line setting for patients newly diagnosed with ALK-positive NSCLC in Canadian practice. The shift from crizotinib to alectinib in the first-line setting occurred in response to the results of the Global ALEX[4] and J ALEX trials[5], where alectinib demonstrated improved PFS compared to crizotinib. Although crizotinib was the most appropriate comparator when the ALTA-1L trial was designed, alectinib is the most commonly used first-line treatment in current Canadian practice.
- The two data cut-off dates of February 19, 2018 and July 28, 2019 represent interim analyses of the ALTA-1L trial. The OS data is immature, with a total of only 70 deaths (25% maturity) reported as of the second interim analysis. Follow-up for long-term survival is ongoing and analysis is planned to be completed in June 2021 as a non-inferential landmark analysis. It should be highlighted that OS was not formally tested in the trial due to data immaturity and median OS has not been reached in either group. As a result, the actual degree of long-term benefit of brigatinib treatment is unknown.
- Overall survival data are confounded by crossover of patients in the crizotinib group to brigatinib and subsequent use of other anticancer therapies (including TKIs) by patients in both groups after discontinuation of the study treatment. Subsequent treatments and crossover may have prolonged survival beyond what would have occurred had the patients only received their randomized study treatment. The ALTA-1L protocol pre-planned exploratory sensitivity analyses to adjust for crossover effects. The following key limitations associated with the analyses were noted. OS data are immature, with a total of only 70 deaths reported as of the second interim analysis, including 33 (24%) patients in the brigatinib group and 37 (27%) patients in the crizotinib group. An abstract reporting the results of these analyses identified limitations due to difficulties validating the

requirements underpinning treatment switching methodologies and not accounting for other subsequent ALK inhibitor use.[6] Given the immature OS data, and likely biases with the treatment switching adjustments analyses methods, the Methods Team cannot firmly conclude that the analyses adequately adjusts for the confounding effects of crossover.

Table 1: Highlights of Key Outcomes in the ALTA-1L Trial

	ALTA-1L Trial			
	First Interim Analysis (data cut-off February 19, 2018)		Secondary Interim Analysis (data cut-off June 28, 2019)	
	Brigatinib (N=137)	Crizotinib (N=138)	Brigatinib (N=137)	Crizotinib (N=138)
Primary Outcome				
PFS by BIRC (ITT population)				
Median (95% CI) in months	NR (NR–NR)	9.8 (9.0–12.9)	24.0 (18.5–NR)	11.0 (9.2–12.9)
HR (95%CI)	0.49 (0.33–0.74)		0.49 (0.35–0.68)	
p-value	< 0.001		< 0.0001*	
Key Secondary Outcomes				
Confirmed ORR by BIRC (ITT population)				
% (95% CI)	71 (62–78)	60 (51–68)	74 (66–81)	62 (53 – 70)
OR (95%CI)	1.59 (0.96–2.62)		1.73 (1.04–2.88)	
p-value	0.0678		0.0342*	
Confirmed intracranial ORR by BIRC (patients with any intracranial CNS metastases at baseline)				
Patients contributing to analysis, n (%)	43 (31)	47 (34)	47 (34)	49 (36)
Median (95% CI) in months	67 (51–81)	17 (8–31)	66 (51–79)	16 (7–30)
OR (95%CI)	13.00 (4.38–38.61)		11.75 (4.19–32.91)	
p-value	< 0.0001*		< 0.0001*	
Intracranial PFS by BIRC (ITT population)				
Median (95% CI) in months	NR (NR–NR)	NR (11.1–NR)	32.3 (29.5–NR)	24.0 (12.9–NR)
HR (95%CI)	0.42 (0.24–0.70)		0.45 (0.29–0.69)	
p-value	0.0011*		0.0001*	
OS (ITT population)				
Median (95% CI) in months	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)
HR (95%CI)	0.98 (0.50–1.93)		0.92 (0.57–1.47)	
p-value	0.9611*		0.771*	
DOR				
Median (95% CI) in months	NR (NR–NR)	11.1 (9.2–NR)	NR (19.4–NR)	13.8 (9.3–20.8)
KM estimated rate of 12-month DOR, % (95% CI)	75 (63–83)	41 (26–54)	78 (68–85)	54 (42–65)
Data cut-off date	**Secondary Interim Analysis (data cut-off June 28, 2019)**			
	Brigatinib (N=137)		**Crizotinib (N=138)**	

	ALTA-1L Trial			
	First Interim Analysis (data cut-off February 19, 2018)		Secondary Interim Analysis (data cut-off June 28, 2019)	
	Brigatinib (N=137)	Crizotinib (N=138)	Brigatinib (N=137)	Crizotinib (N=138)
Change from baseline in GHS/QOL by EORTC QLQ-C30 (patients with a baseline and ≥ 1 post-baseline assessment)				
Patients contributing to analysis, n (%)	131 (96)		131 (95)	
Time to worsening of GHS/QoL score by ≥10 points				
Median (95% CI) in months	26.7 (8.3–NR)		8.3 (5.7–13.5)	
HR (95%CI)	0.70 (0.49–1.00)			
p-value	0.049*			
Duration of improvement in GHS/QoL score by ≥10 points				
n (%)	79 (60)		83 (63)	
Median (95% CI) in months	NR (NR–NR)		12.0 (7.7–17.5)	
HR (95%CI)	0.27 (0.14–0.49)			
p-value	< 0.0001*			
Time to worsening of dyspnea by EORTC QLQ-LC13 (patients with a baseline and ≥ 1 post-baseline assessment)				
Patients contributing to analysis, n (%)	63 (46)		78 (57)	
Time to worsening of dyspnea (50% decline from baseline)				
n (%)	14 (22)		26 (33)	
Median (95% CI) in months	NR (NR–NR)		NR (17.1–NR)	
HR (95%CI)	0.54 (0.28–1.04)			
p-value	0.0658*			
Harms, n (%)				
TEAE (any grade)	135 (99)		137 (100)	
TEAE grade ≥ 3	90 (66)		73 (53)	
TEAE leading to treatment interruption	17 (13)		12 (9)	
TEAE leading to dose reduction	52 (38)		34 (25)	
TEAE leading to treatment discontinuation	90 (66)		64 (47)	
SAE	45 (33)		51 (37)	

AE = adverse event, BIRC = blinded independent review committee, CI = confidence interval, CNS = central nervous system, EORTC QLQ= European Organization for Research and Treatment of Cancer quality of life questionnaire, GHS = global health status, HR = hazard ratio, HRQoL = health-related quality of life, ITT = intention-to-treat, KM = Kaplan-Meier, NA = not applicable, NR = not reached, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QoL = quality of life, SAE = serious adverse event, SD = standard deviation, TEAE = treatment-emergent adverse event

* Nominal P value (non-inferential)

HR < 1 favours the brigatinib group

Data sources: Camidge at al. 2018,[1] Camidge et al. 2020,[2] EPAR 2020[7], Clinical Study Report

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

One input was provided by Lung Cancer Canada (LCC) for the review of Brigatinib (Alunbrig) for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor. Currently, there are a number of targeted therapies such as alectinib and crizotinib to treat patients with ALK-positive NSCLC. According to the input received, current therapies, allow patients to be functional and active, have a good QoL, live longer, and improve their prognosis and survival rates. Crizotinib was the first efficacious option for ALK-positive NSCLC. Many respondents on this treatment have reported being active and highly functioning. Reported side effects on crizotinib were nausea, vomiting, diarrhea, visual disturbances, edema and fatigue. Some patients did find the side effects intolerable. Alectinib is publicly covered as a first- and second-line treatment option. This treatment has presented better efficacy and lower toxicity compared to crizotinib. It has been found to be effective in treating patients with brain metastases, thus reducing or eliminating the need for whole brain radiation. It is generally very well tolerated with manageable side effects.

Patients with the ALK mutation commonly present with brain metastases at diagnosis; this has been observed in about 30% of patients and can limit their survival. Brain metastases can be quite debilitating, affecting patient QoL and resulting in a poorer prognosis. Crizotinib has a lower efficacy particularly with CNS involvement, however alectinib has been found to be effective in treating patients with brain metastases. While currently options exist to treat ALK positive NSCLC in the first line, there is an unmet need to provide treatments that are effective in treating brain involvement and delaying progression.

Improved outcomes expected from new therapies reported by patient respondents included being effective at treating CNS metastases, improved symptoms, prolonged survival, a good QoL, manageable side effects, longer lasting durable treatment and delayed progression of disease.

Two patient respondents spoke to their experiences with brigatinib as a first-line treatment. They commented on how brigatinib has controlled their cancer, reduced the size of their tumors and allowed them to live a productive and fulfilling life. Common side effects reported by respondents of the drug under review include fatigue, vomiting, diarrhea, constipation, abdominal pain and muscle and joint pain.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Time-limited need for patients receiving treatment with either crizotinib or alectinib
- Sequencing and priority of treatments

Economic factors:

- None

Registered Clinician Input

A total of two registered joint clinician inputs were provided on behalf of three clinicians from Ontario Health Cancer Care Ontario (CCO) and 13 clinicians from LCC for the review of brigatinib (Alunbrig) indicated for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who were previously untreated with an ALK inhibitor.

Lung Cancer Canada stated that of the current treatments available, crizotinib and ceritinib are no longer considered appropriate comparators for the drug under review. Both clinician groups indicated that the most appropriate comparator in the first-line setting is alectinib.

Both clinician groups stated that they would prescribe brigatinib to patients with advanced ALK-positive NSCLC in the first line setting. Clinicians from CCO, stated that because alectinib is already used in the first line, brigatinib would be an additional option, and there is not an unmet need. In contrast, clinicians from LCC indicated that there is a significant unmet need for additional ALK-

targeting agents in all lines of therapy, including first line. In the event that alectinib is not available, it would be beneficial to have another option.

Both clinician groups had experience using brigatinib and described how they would use brigatinib in the first line setting as an alternative to alectinib. Clinicians from LCC stated that given the prevalent and established use of alectinib in the first-line setting, and its dominance over early generation ALK TKIs such as crizotinib and ceritinib, brigatinib will likely be used in the first-line setting under specific circumstances when an alternative is preferred or required (i.e., toxicity by alectinib). The selection of brigatinib as a first line therapy may be preferred due to its efficacy in treating brain metastases at baseline. Brigatinib has higher Grade 3+ toxicities than alectinib. The difference is mostly related to deranged biochemical parameters (CK, liver enzyme, amylase elevations) of unknown significance, which can lead to higher rates of dose interruptions and dose reductions. Brigatinib has similar low toxicity-related treatment discontinuation rates as alectinib. According to clinicians, both drugs are well tolerated by patients. Both clinician groups stated that ALK testing has been standardized in Canada and as a result, jurisdictions across Canada have uniformly adopted its use in routine lung biomarker testing.

Summary of Supplemental Questions

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators. Consequently, the sponsor provided indirect treatment comparisons (ITCs) using matched adjusted indirect comparisons (MAICs) and the Bucher ITC method of relevant comparators, which were identified based on a systematic review of treatments for locally advanced or metastatic ALK-positive NSCLC.[8] The focus of the ITCs was to compare 1) brigatinib and alectinib via MAICs (both anchored and unanchored) and the Bucher ITC method (including the ALTA-1L[9] and ALEX[4] trials) and 2) brigatinib and ceritinib via MAICs (including the ALTA-1L[9] and ASCEND-4[10] trials). The ITCs derived comparative estimates for the outcomes of OS, ORR, PFS, and DOR. The results were not statistically significantly different between brigatinib and alectinib for OS, ORR, PFS, and DOR. The methods and results of the ITCs were critically appraised by the pCODR Methods Team according to best practice principles for MAICs.[11] The results did not favour brigatinib over alectinib or brigatinib over ceritinib for any of the outcomes, except for PFS as per investigator assessment in the comparison of brigatinib versus ceritinib, which demonstrated statistically significant results in favour of brigatinib over ceritinib. The pCODR Methods Team concluded that results should be interpreted with consideration of the several limitations associated with the analyses, such as heterogeneity between studies, inability to adjust for all potential confounders and prognostic variables and use of inappropriate analysis methods for MAIC (e.g., not providing residual bias estimates for MAICs). The ITCs were performed by a consultancy group hired by the sponsor. As a result, the information provided in the reports should be viewed considering this potential conflict of interest. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with brigatinib.

In addition to the sponsor-provided ITCs, the CADTH Methods Team identified two published ITCs by Elliott et al.[12] and Ando et al.[13] The focus of the network meta-analysis (NMA) by Elliott et al.[12] was to examine the relative effects of ALK-inhibitors among patients with ALK- or ROS1-positive NSCLC. Overall, thirteen trials were included in the published NMA of ALK-inhibitors for NSCLC. The ALK-inhibitors examined were crizotinib, alectinib, ceritinib, and brigatinib. For OS and PFS no differences were observed between alectinib and brigatinib. Comparisons between alectinib and brigatinib were not available for the other outcomes (treatment-related deaths and SAEs). The CADTH Methods Team performed a critical appraisal and noted that the principal limitations of the NMA concerned dearth of RCTs (only 8-10 per NMA) available on ALK-inhibitors for NSCLC and the fact that cross-over was allowed after disease progression in half of the included RCTs, which could have confounded the results for OS and was unable to be adjusted for due to the lack of individual patient data (IPD) available. As well, some heterogeneity was observed in baseline characteristics across the studies and not all were adjusted for in the analyses. For example, baseline brain CNS metastases varied across the trials, yet this was not adjusted for. A sub-group analysis was only conducted for treatment-naïve versus treatment-experienced patients. PFS is a surrogate outcome for OS and may be prone to measurement error and bias. Indeed, most RCTs that reported PFS employed an independent review committee to ascertain disease progression, yet three RCTs used unblinded assessment as per the trial investigators. Another limitation is that due to the small number of included trials, publication bias was not assessed. These limitations result in imprecision of estimates and uncertainty of results. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

The focus of the NMA by Ando et al.[13] was to examine the relative effects of brigatinib compared with alectinib among patients with ALK-positive NSCLC with or without CNS metastases. Three trials were included in the analyses. The ALK-inhibitors examined were crizotinib, alectinib, and brigatinib. The analyses included comparative estimates for outcomes of PFS and grade 3-5 AEs. For both PFS and grade 3-5 AEs, no differences were observed between alectinib and brigatinib. The CADTH Methods Team performed a critical appraisal and noted that the systematic review methods were unclear, with limitations such as not reporting the number of researchers conducting screening, data abstraction, and risk of bias appraisal. Heterogeneity between the RCTs was not reported, nor was examination of the transitivity assumption. As well, it was not reported whether a random effects or fixed effect model was used. The principal limitations of the NMA concern dearth of RCTs available on ALK-inhibitors, that no closed loops were available to assess consistency, and that other ALK-inhibitors were excluded from the analysis. These limitations result in imprecision of estimates and uncertainty of results. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

The CADTH Methods Team identified an additional poster (Lin et al. 2021)[14] which is publicly available on the International Association for the Study of Lung Cancer (IASLC) 2020 conference website that reported on indirect treatment comparisons of brigatinib compared to other approved ALK inhibitors or chemotherapy. Due to the limited information available from the abstract, the CADTH Methods Team was not able to perform a critical assessment and to provide detailed summaries. While the CADTH Review Team acknowledges receipt of the full NMA report the sponsor was informed about and consented to there being insufficient time to perform a review and critical appraisal of the full report by the CADTH Methods Team within the regular review timelines. The outcomes included in the Lin et al. (2021)[14] abstract included OS and PFS (both independent review assessed and investigator assessed). In addition, sensitivity analysis was reported by no prior chemotherapy and baseline CNS brain metastases for PFS results only. For the OS outcome, no significant differences between brigatinib and all comparators were reported (specific results not reported in the abstract). For brigatinib versus alectinib, no significant differences were observed for independent review assessed PFS or investigator-assessed for overall patients. For the sub-group with no prior chemotherapy, the results were consistent. Results were also consistent for the sensitivity analysis restricted to those with baseline brain CNS metastases for investigator assessed PFS; results were not provided for this analysis for independent review assessed PFS.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

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

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

Domain	Factor	Evidence from ALTA-1L trial	Generalizability Question	CGP Assessment of Generalizability
	Organ Dysfunction	The ALTA-1L trial limited eligibility to patients with adequate renal, hepatic, and bone marrow function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice)?	Given the tolerable safety profile of brigatinib the CGP recommends discretion of the treating physician for use of brigatinib in patients with lab parameters beyond those outlined in the trial.
	Dose and Schedule	Brigatinib was administered at a dose of 180 mg orally once daily after a 7-day lead-in period of 90 mg orally once daily. Crizotinib was administered at a dose of 250 mg orally twice daily.	Is the trial dosage generalizable to patients across Canada?	The dose of brigatinib in the ALTA-1L trial is fully applicable to Canadian clinical practice and aligns with the dose recommended by Health Canada.
Outcomes	Appropriateness of primary and secondary outcomes	Primary: • PFS by BIRC Secondary: • ORR by BIRC • Intracranial ORR by BIRC • Intracranial PFS by BIRC • OS • DOR by BIRC • TTR by BIRC • DCR by BIRC • Safety and tolerability • HRQoL (EORTC QLQ-C30 and EORTC QLQ-LC13)	Were the primary and secondary outcomes appropriate for the trial design?	While PFS has not been validated as a surrogate endpoint for either overall survival or quality of life in NSCLC in the advanced NSCLC setting, PFS is an established outcome in this setting and is used by Canadian clinicians to guide treatment selection. According to the CGP's clinical experience, as well as the inputs from the patient advocacy group and registered clinicians indicated that cancer progression – CNS progression and extra-CNS progression – is a highly relevant

Domain	Factor	Evidence from ALTA-1L trial	Generalizability Question	CGP Assessment of Generalizability
				clinical issue in patients in this setting. Reducing CNS metastases and delaying disease progression is a very important goal and is likely to lead to a lengthened life with improved quality. CNS metastases may require radiation therapy potentially resulting in cognitive deficits, may be associated with significant morbidity and are of an unpredictable nature, making their prevention and control an important clinical goal. Response rate and OS are reasonable secondary outcomes for this study. The CGP feels that the response rate reflects the ability of therapy to inhibit the target and consequently would be associated with benefit.
Setting	Countries participating in the trial	ALTA-1L was a global trial that enrolled 275 patients from 19 countries: • 143 patients from Europe (Austria, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom) • 107 patients from the Asia Pacific region (Australia, Hong Kong, Taiwan, Singapore, and South Korea) • 25 patients from North America (US and Canada)	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?	Overall, most patients were from Europe and Asia where practice patterns would be similar to Canada. The CGP agree that the populations where the trials were conducted would be comparable to the Canadian population and therefore the results of the trial would be generalizable to the

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ALTA-1L trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>Two Canadian patients were randomized.

Race subgroups assessed in the trial:
<table>
<tr><td colspan="3">Race, N (%)</td></tr>
<tr><td></td><td>Brigatinib (N=137)</td><td>Crizotinib (N=138)</td></tr>
<tr><td>Asian</td><td>59 (43)</td><td>49 (36)</td></tr>
<tr><td>Non-Asian</td><td>78 (57)</td><td>89 (64)</td></tr>
<tr><td>White</td><td>76 (55)</td><td>86 (62)</td></tr>
<tr><td>Black</td><td>0 (0)</td><td>2 (1)</td></tr>
<tr><td>Unknown</td><td>2 (1)</td><td>1 (1)</td></tr>
</table>
<table>
<tr><td colspan="3">PFS by BIRC for race subgroups</td></tr>
<tr><td></td><td colspan="2">HR (95% CI)</td></tr>
<tr><td></td><td>First Interim Analysis</td><td>Second Interim Analysis</td></tr>
<tr><td>Asian</td><td>0.41 (0.20 –0.86)</td><td>0.38 (0.22 – 0.65)</td></tr>
<tr><td>Non-Asian</td><td>0.54 (0.33 –0.90)</td><td>0.54 (0.36 – 0.83</td></tr>
</table></td><td></td><td>broader Canadian population. The CGP cautioned that there may be inter-country differences in the availability of subsequent treatments after progression on brigatinib.</td></tr>
<tr><td></td><td>Supportive medications, procedures, or care</td><td>The type and frequency of concomitant medication received in ALTA-1L trial was comparable between the study groups. The most frequently received concomitant medications in both study groups included paracetamol, dexamethasone, omeprazole, furosemide, metoclopramide hydrochloride, and loperamide hydrochloride.</td><td>Are the results of the trial generalizable to a setting where different supportive medications or care are used?</td><td>The use of concomitant medication reported in the ALTA-1L trial is as expected for the population of advanced or metastatic NSCLC. The CGP agreed that the support medications given in the trial are generalizable to the majority of Canadian treatment centres.</td></tr>
</table>

Abbreviations: BIRC = blinded independent review committee, CGP = CADTH clinical guidance panel, DCR = disease control rate; DOR = duration of response, HR = hazard ratio, HRQoL=health-related quality of life, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS= overall survival, PFS = progression-free survival, TTR = time to response

1.2.4 Interpretation

Burden of Illness

Although no national data are available for Canadian patients, the French Cooperative Thoracic Intergroup (IFCT) reported a 5% ALK positivity in 8,134 patients assessed in a one-year period.[15] Given that lung cancer rates and smoking rates are similar between Canada and France, a 3%-5% incidence is a reasonable assumption for Canada. Roughly 20,000 patients per year die of lung cancer in Canada[16] and the majority with advanced disease. Based on these figures, the estimated number of new ALK positive advanced lung cancer patients annually would be 600-800. ALK positive lung cancer, in contrast to the majority of lung cancer in Canada, is a disease that develops in people independent of tobacco exposure and in younger patients. Unfortunately, as a disease without any known risk factors, there are no methods of prevention or early detection. Tobacco control efforts and early lung cancer screening programs are not expected to alter the burden of ALK positive advanced lung cancer.

Central nervous system metastases are 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.[17]

Current Practice Patterns in Canada and Clinical Need

Determination of ALK positivity by immunohistochemistry or other methods is standard practice for advanced non-squamous NSCLC. Alectinib is the currently accepted first line option for metastatic ALK positive NSCLC in Canada. Alectinib is recommended as such in various practice guidelines and is funded for this indication.

Due to the strong association between ALK positive NSCLC and development of brain metastasis, there is a strong need for agents that are effective in management of CNS disease. Alectinib meets this requirement, but there is a need for alternatives. Drug selection needs to take into consideration patient characteristics and the side effect profile of different agents. Brigatinib satisfies the need for an ALK inhibitor more effective than crizotinib as well as having good CNS activity. As with most conditions, it's beneficial to have more than one option for treatment from both a supply chain perspective (i.e., interruptions in supply from one manufacturer) and from a patient tolerance perspective.

Effectiveness

The primary endpoint of the ALTA-1L trial was PFS by BIRC and the key secondary endpoints tested hierarchically are confirmed ORR, intracranial ORR, intracranial PFS, and OS. PFS is an established outcome in the current setting and is used by Canadian clinicians to guide treatment selection. The key secondary endpoints are also appropriate, as systemic and intracranial response to treatment are clinically relevant endpoints given the high risk of brain metastases with ALK+ NSCLC. Overall, the baseline characteristics were reflective of the patient population in the target indication with no clinically important imbalances between the study groups. The primary endpoint was met in the ALTA-1L study at the first interim analysis. Updated PFS data at the second interim analysis showed consistent results with those at the first interim analysis in favor of brigatinib (absolute difference of 13 months improvement in PFS with brigatinib), which are clinically meaningful results in this incurable disease setting.

Confirmed ORR by BIRC suggested a trend in favour of brigatinib and prolonged duration of response as well as a marked improvement in intracranial ORR compared with crizotinib; supported by intracranial PFS. These results reflect the ability of brigatinib to inhibit the target and are important because they translate into better disease control and symptom relief.

Median OS was not reached in either study group and may be confounded by cross-over to brigatinib from the crizotinib group and subsequent lines of therapy, which includes other ALK inhibitors and platinum-based combination chemotherapy.

Results of exploratory subgroup analyses for PFS by previous chemotherapy (yes/no) were consistent with the overall estimates of PFS favoring brigatinib. One line of prior chemotherapy was allowed in the inclusion criteria which seems reasonable for the requested reimbursement indication.

Harms, Safety and Tolerability

Exploratory patient-reported outcomes data suggest that brigatinib is associated with a longer duration of improvement in quality of life compared to crizotinib. Contributing to this benefit is the efficacy of brigatinib in management of CNS disease, with a marked delay in progression of brain metastasis.

Treatment with brigatinib does result in more dose interruptions than crizotinib, but the frequency of treatment discontinuation is similar. Overall, the spectrum of side effects associated with brigatinib is comparable to other ALK inhibitors, although there are notable differences in the risk of certain toxicities compared to alectinib. Most notable are that brigatinib is associated with a higher risk for pulmonary toxicity and hypertension, but a lower risk of peripheral edema, weight gain, and cytopenias.

Comparative Therapies considered

Currently, only indirect comparisons can be made between brigatinib and alectinib as no trial to date has directly compared these drugs as first-line therapy for patients with ALK-positive locally advanced or metastatic NSCLC who were previously untreated with an ALK inhibitor. Refer to Section 7 for summaries and critical appraisals of one sponsor-submitted and two published ITCs (Elliott et al. [2020][12] and Ando et al. [2020][13]). The CGP noted that the sponsor-submitted ITCs suggested that the results were not statistically significant different between brigatinib and alectinib for OS, ORR, PFS, and DOR. The results of the published ITC by Elliott et al.[12] suggested as well that there was no difference between brigatinib and alectinib for OS and PFS. The published results by Ando et al.[13] were consistent, suggesting no statistically significant difference between brigatinib and alectinib for PFS (OS was not reported). In addition, Ando et al. reported that no difference was observed for grade 3 to 5 adverse events between brigatinib and alectinib. However, the CGP agreed with the CADTH Methods Team, that due to several limitations identified in the ITCs caution must be used in interpreting the comparative efficacy estimates. Given the absence of a direct comparison, there is no robust evidence to ascertain which of the agents (i.e., brigatinib or alectinib) has superior efficacy or a better safety profile. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to brigatinib compared with crizotinib for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor This conclusion is based on evidence from the ALTA-1L trial, that demonstrated clinically meaningful and statistically significant benefits in PFS, improvements in confirmed ORR and intracranial ORR in favour of brigatinib, and a manageable safety profile that was supported by patient reported outcomes.

The CGP acknowledges uncertainty regarding any advantage of brigatinib over alectinib, which previously supplanted crizotinib as the preferred first line ALK inhibitor in routine clinical practice in Canada. However, it is also uncertain that alectinib has any advantage over brigatinib in the absence of a randomized trial comparing both agents against each other. As with most conditions, it's beneficial to have more than one option for treatment from both a patient tolerance perspective and a supply chain perspective (i.e., interruptions in supply from one manufacturer).

The CGP considered the following:

- There is a clear general advantage of brigatinib over crizotinib in terms of progression free survival, the primary endpoint of the ALTA-1L trial, as well as secondary endpoints that included objective tumour response rate, disease control rate, duration of response, and patient reported quality of life.
- As well, in favour of use of brigatinib as first line therapy is its efficacy in management of CNS disease, which is a significant issue in patients with ALK positive NSCLC.
- There is a clear advantage of brigatinib over crizotinib when considering control of CNS disease, again in terms of objective tumour response rate, disease control rate, and duration of response.
- However, overall survival data in the ALTA-1L trial is immature. It is uncertain if an overall survival benefit will be seen in long term follow up, as results are likely to be confounded by the effectiveness of subsequent lines of therapy, which includes other ALK inhibitors and platinum-based combination chemotherapy.
- Lacking data directly comparing brigatinib to alectinib, clinicians will favour alectinib based on current drug accessibility, and familiarity with its efficacy and side effects in their personal clinical practice. However, differences in the side effect profiles of brigatinib and alectinib are expected to influence the selection of treatment on a case-by-case basis.
- In addition, the severity of side effects from one agent may necessitate its discontinuation, and a switch to another ALK inhibitor is routine practice. Currently, alectinib would be switched to crizotinib in most instances, which might be better tolerated but would be less effective. It would be more appropriate to use brigatinib if alectinib were not tolerated, and vice versa.

- In some instances, chemotherapy and/or immunotherapy may have been initiated prior to reporting of ALK mutation status. If so, it would be appropriate to switch to an ALK inhibitor like brigatinib.
- As with alectinib, at the time brigatinib is discontinued due to disease progression, it is currently uncertain if it would be appropriate to use another ALK inhibitor as second line therapy. However, as with alectinib, it is expected that clinicians would use a more effective ALK inhibitor like brigatinib in the second line setting, rather than an older less effective agent like crizotinib.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
Currently Funded Treatments	
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with brigatinib:	
• patients that previously received more than one systemic anticancer therapy regimen for advanced disease	• Patients were eligible to enter the ALTA-1L trial if they had received no more than one prior systemic anticancer therapy regimen for locally advanced or metastatic disease. Overall, 27% of patients had received previous chemotherapy. Of these patients the majority had received chemotherapy for advanced or metastatic disease and few patients had received neoadjuvant and/or adjuvant chemotherapy. The CGP noted that the benefit of treatment with brigatinib was seen in patients regardless of whether they had received one prior line of chemotherapy or not and felt that it would be reasonable to generalize the results to patients who have received more than one line of previous chemotherapy for locally advanced or metastatic disease. However, the CGP agreed that patients should not have previously been treated with an ALK inhibitor such as crizotinib or alectinib.
• patients who received chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days before the first dose of brigatinib	• The ALTA-1L trial limited trial eligibility to patients who had not received chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days of first dose of study drug. The CGP agreed with the trial eligibility criteria and noted there is insufficient evidence to offer brigatinib to patients who had received chemotherapy or radiation therapy withing 14 days before the first dose of brigatinib. In particular, the CGP noted concerns about treating sooner in patients who have had radiation therapy to the chest because of potential toxicities with brigatinib.
• patients with ECOG PS>2.	• The ALTA-1L trial included patients with ECOG PS of 2 or less. Most patients in the trial had ECOG PS of 0 or 1. The CGP noted that approximately a quarter to a third of the patients seen in clinical practice have worse performance status than patients included in the ALTLA-1L trial (ECOG greater than 2). While the CGP agreed that the benefit for patients with an ECOG status of greater than 2 cannot be formally concluded from the ALTA-1L trial, the CGP felt it

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
• patients with symptomatic CNS metastases	would be reasonable to offer brigatinib to patients with ECOG PS of greater than 2 in patients whose ECOG PS may be related to the underlying disease or tumour symptoms. • The ALTA-1L trial limited eligibility to patients with asymptomatic CNS metastases as long as patients did not require an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization. Exploratory subgroup analyses in the ALTA-1L trial suggested that brigatinib was associated with improvements in PFS compared to crizotinib in patients with and without intracranial CNS metastases at baseline. The CGP felt it would be reasonable to offer brigatinib to patients with and without brain metastases, whether symptomatic or asymptomatic at baseline. The CGP recommended discretion of the treating physician for use of systemic therapy (i.e., brigatinib) or radiotherapy in patients with symptomatic CNS disease. Possible considerations may include the size of the brain metastases (if smaller, then an ALK inhibitor might be preferred, leaving radiotherapy as a backup option), the time it will take to arrange a radiation oncology consultation (if it takes time to arrange consultation, then the default strategy is to start ALK inhibitor), and the activity of non-CNS disease (if symptomatic from non-CNS disease, systemic therapy would usually be initiated as soon as possible)
PAG is seeking advice on a time-limited need to cover patients who were receiving treatment with crizotinib or alectinib and may be better candidates for treatment with brigatinib.	The CGP noted that it would be reasonable to offer brigatinib on a time-limited basis to patients who have recently started crizotinib therapy because alectinib was not accessible to them. However, if patients have been receiving crizotinib for a longer period of time and are doing well, switching these patients from crizotinib to brigatinib would not be indicated. The CGP noted that alectinib is currently funded in all provinces in Canada, except Prince Edward Island. The CGP noted that there is insufficient evidence to ascertain the treatment effect of brigatinib in patients who have started treatment with alectinib. Furthermore, the CGP noted that there is currently no robust evidence to ascertain which of the agents (i.e., brigatinib or alectinib) has superior efficacy. For these reasons the CGP does not support offering brigatinib on a time-limited basis in patients who are currently receiving alectinib and have not progressed.
PAG is concerned by the potential indication creep on the following scenarios: use in second line or later settings, use in neoadjuvant or adjuvant treatment of resectable NSCLC.	The CGP noted that there is insufficient evidence to extrapolate the trial results to second line ALK inhibitor or later settings, or to the management of neoadjuvant or adjuvant resectable NSCLC disease.
Implementation Factors	
PAG is seeking clarity on treatment until “disease progression” and “unacceptable toxicity.”	Treatment continued in the ALTA-1L trial until disease progression or intolerable toxicity. Tumor response assessments were conducted every 8 weeks and assessed per RECIST v1.1 by the BIRC and the investigator until BIRC-assessed disease progression. After experiencing progressive disease, participants in the brigatinib group could continue the

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	study treatment if they continued to experience clinical benefit in the opinion of the investigator. For patients who continued brigatinib beyond disease progression, tumor assessments continued to be performed every 8 weeks. In NSCLC with molecular aberrations and effective targeted agents, Canadian clinical practice is to treat until lack of clinical benefit (progressive, symptomatic disease). The CGP agreed that the trial parameters in the ALTA-1L trial set for treatment discontinuation are reasonable and reflective of clinical practice. The CGP noted that with long duration of therapy, there is tumor evolution and increased tumor heterogeneity. This may result in control for the majority disease but progression in selected areas; oligo-progression. In practice, oligo-progression is often treated locally with radiotherapy, ablative options or surgery with ongoing ALK inhibitor therapy.
Sequencing and Priority of Treatment	
• What treatment options would be available to patients who progressed on brigatinib?	• The CGP noted that there is currently no clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with brigatinib. Possible treatment options could include chemotherapy (i.e., a platinum/pemetrexed doublet chemotherapy) or other ALK TKIs (e.g., lorlatinib) options if available.
• What evidence is there to inform the sequencing of alectinib or other ALK TKIs after first line brigatinib?	• The CGP noted that there is currently no clinical trial evidence to inform the sequencing of alectinib or other ALK TKIs after first line brigatinib.
What treatment options would be available to patients who discontinued brigatinib in the case of toxicity?	In the absence of sufficient evidence to inform this situation the CGP felt that intolerance to any ALK inhibitor in the first line setting (crizotinib or alectinib) would be reasonable grounds for consideration of brigatinib and vice versa. It is recognized that the ALK inhibitors have differences in their toxicity profiles and patients may have better side effect profiles with an alternate to allow ongoing disease control.
If brigatinib is reimbursed, is there a preference for brigatinib or alectinib in the first line setting? What circumstances would first line brigatinib be preferred over first line alectinib?	The CGP noted that given the absence of a direct comparison, there is no robust evidence to ascertain which of the agents (i.e., brigatinib or alectinib) has superior efficacy or a better safety profile. The CGP anticipated that some clinicians may prefer using alectinib as the trial evidence for alectinib has longer follow-up time (median follow-up time in ALEX trial was 37.8 months) than the trial evidence for brigatinib (median follow-up time in the ALTA-1L trial was 24.9 months). In addition, Canadian clinicians are generally more experienced with alectinib than with brigatinib. The CGP felt that intolerance to any ALK inhibitor in the first line setting (crizotinib or alectinib) would be reasonable grounds for consideration of brigatinib and vice versa. Situations in which there would be preference to use alectinib may include patients who have baseline dyspnea or hypoxia (given the rare complication of an early onset pulmonary event), or poorly controlled hypertension. Alternatively, there may be a preference to use brigatinib if there

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	are concerns about the development of weight gain, peripheral edema, myalgia, constipation, and blurry vision.

ALK = anaplastic lymphoma kinase, BIRC = blinded independent review committee; CGP = Clinical Guidance Panel, CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status, ITC = indirect treatment comparison, NSCLC = non-small cell lung cancer, PAG = Provincial Advisory Group, PFS = progression-fee survival; TKI = tyrosine kinase inhibitors

2 Background Clinical Information

2.1 Description of the Condition

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada. Survival from lung cancer is poor, with a five-year net survival of 19%. In 2020 alone, it is estimated that there will be 29,800 new cases of lung cancer diagnosed and 21,200 deaths associated with lung cancer.[16] It is estimated that 1 in 17 Canadians will die from lung cancer.[18] NSCLC represents approximately 85% of all lung cancer cases and, for the purposes of therapeutic decision, cases are categorized by histologic subtype as squamous cell carcinoma, adenocarcinoma, or large cell carcinoma.[16] Adenocarcinoma is the most common type, accounting for 48% of cases in Canada. The majority of patients with NSCLC will present with or develop advanced/metastatic disease and the 5-year relative overall survival rate of patient with NSCLC has been estimated to be 25%.[19] 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). In these cases, the product of the fusion ALK gene acts as an oncogenic driver. Certain clinical characteristics are more likely to be associated with ALK-positive NSCLC, including younger age at diagnosis, never or light smoking history, and adenocarcinoma histology.[20] Worldwide, it is estimated that 3-5% of NSCLC patients have ALK rearrangements.[21,22] In Canada, approximately 2.5% of non-squamous NSCLC patients are ALK-positive.[23] Central nervous system (CNS) metastases are 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.[17]

2.2 Accepted Clinical Practice

First-line

There are five agents that have been evaluated in phase III trials in the first-line setting for ALK-positive NSCLC: crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib.

Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, was the first approved therapy for first-line for metastatic ALK-positive NSCLC in Canada. This was based on an open-label phase III study that confirmed superior objective response rates (74% vs. 45%; *P*<0.001) and PFS [median, 10.9 months vs. 7.0 months; hazard ratio (HR) for progression or death with crizotinib, 0.45; 95% CI, 0.35–0.60; *P* < 0.001] favouring crizotinib when compared to first-line platinum doublet chemotherapy.[24] Overall survival was not different between the two groups, likely due to the high rate of cross-over to crizotinib in the chemotherapy group.[24] 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 the PROFILE 1014 trial, 73% of patients were treated beyond progression with crizotinib, for a median of 3.1 months. The CNS appears to be a common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS. If the CNS is the only site of progression, local therapy with radiation is often used to treat the site(s) of progression and crizotinib is continued. Crizotinib is publicly funded for first-line treatment in all provinces.

The second generation ALK inhibitor, ceritinib, has also been evaluated in the first line setting. The ASCEND 4 trial compared oral ceritinib 750 mg/day to platinum-based chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5–6 plus pemetrexed 500 mg/m^2 every 3 weeks for four cycles) followed by maintenance pemetrexed in ALK-positive treatment naïve patients.[25] Three hundred and seventy six patients were randomly assigned to ceritinib (N = 189) and chemotherapy (N = 187). The primary endpoint was BIRC assessed PFS, which was 16.6 months (95% CI, 12.6 – 27.2) in the ceritinib group and 8.1 months (95% CI, 5.8 – 11.1) in the chemotherapy group (HR, 0.55; 95% CI, 0.42 – 0.73; *P* < 0.00001).[25] Ceritinib is Health Canada-approved in the first-line setting but has not been submitted to CADTH for review.

Alectinib is a second generation ALK inhibitor that was evaluated in the first-line setting against crizotinib in two phase III trials: J ALEX[5] and Global ALEX.[4] J ALEX was conducted exclusively in Japan and patients were randomized to alectinib 300 mg twice daily or crizotinib 250 mg twice daily until progressive disease, unacceptable toxicity, death, or withdrawal. The primary endpoint was BIRC-assessed PFS. Two hundred and seven patients were recruited and assigned to the alectinib (N = 103) or crizotinib (N = 104)

groups. At the second interim analysis, an independent data monitoring committee determined that the primary endpoint of the study had been met (HR, 0.34; 99.7% CI, 0.17 – 0.71; stratified log-rank *P*<0.0001) and recommended an immediate release of the data. Median PFS had was not reached with alectinib and was 10.2 months (95% CI, 8.2 – 12.0) with crizotinib. This head-to-head comparison of alectinib to crizotinib in a Japanese population demonstrated superior outcomes with alectinib. The Global ALEX trial[4] of alectinib 600 mg twice daily versus crizotinib 250 mg twice daily confirmed the findings of J ALEX. It is notable that the dose in the global study was double that used in the Japanese study. One hundred and fifty-two patients were randomized to the alectinib group and 151 patients to the crizotinib group. Most patients were treated at trial sites in Asia (50%), Europe (26%), and North America (16%). The trial met its primary endpoint for efficacy; median PFS by investigator assessment was 34.8 months in the alectinib group and 10.8 months in the crizotinib group (stratified HR, 0.43; 95% CI, 0.32 – 0.58).[26] Time-to-CNS progression was significantly longer in the alectinib treatment group (HR, 0.16; 95% CI, 0.10 – 0.28; *P* < 0.001), regardless of CNS metastasis status at baseline. The difference in CNS ORR between the treatment groups was statistically significant (OR, 4.05; 95% CI, 1.89 – 8.70; P = 0.0002). The combination of the J-ALEX and Global ALEX trial confirmed the benefit of alectinib in the first line setting and has been recommended by CADTH for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC. Based on the impressive PFS compared to crizotinib, alectinib is now the ALK inhibitor of choice in the first line setting for newly diagnosed patients and is currently publicly funded in most provinces.

Lorlatinib is a third generation ALK inhibitor that is currently being evaluated as a first-line treatment for ALK-positive NSCLC in an ongoing phase III trial.[27] The international CROWN trial randomized 296 patients in a 1:1 ratio to either 100 mg lorlatinib once daily or 250 mg crizotinib twice daily. Results of a planned interim analysis have been reported in a conference abstract. As of the interim analysis, PFS by BIRC was not reached (NR) (95% CI, NR–NR) in the lorlatinib group versus 9.3 months (95% CI, 7.6–11.1) in the crizotinib group (HR, 0.28; 95% CI, 0.191–0.413; *P* < 0.001). Lorlatinib monotherapy for ALK-positive NSCLC in the first-line setting has not been submitted to CADTH for review.

Due to the longer use of crizotinib as first-line therapy, there is a better understanding of resistance mechanisms against this agent. On-target genetic alterations, including ALK mutations and ALK amplification, account for 30% of resistance.[28] Off-target mechanisms of resistance include upregulation of other signaling pathways. Molecular characterization of crizotinib resistant patients identified a resistance mutation in 20%: L1196M (7%), G1269A (4%), C1156Y (2%), G1202R (2%), I1171T (2%), S1206Y (2%), and E1210K (2%). The most common ALK mutations were G1202R (21%), F1174C/L (16.7%), and C1156Y (8%) in patients treated with ceritinib and crizotinib.[29] There is less data regarding resistance mechanisms to alectinib however, genetic sequencing identified a resistance mutation in 53%: G1202R (29%), I1171T/S (12%), V1180L (6%), and L1196M (6%). The resistant mutations are relevant when considering second-line therapy, as different agents have different capabilities of addressing these ALK fusion protein changes.

The activity of check-point inhibitors is largely unknown as very few ALK-positive patients were included in the check-point inhibitor clinical trials. The IMpower 150 trial[30] included patients with driver mutations and evaluated bevacizumab, carboplatin, and paclitaxel plus or minus atezolizumab as first-line chemotherapy treatment. However, only 37 ALK-positive patients were included. CHECKMATE 057, KEYNOTE 010 and OAK evaluated single agent immunotherapy versus chemotherapy in the second line setting but only accrued a small number of ALK-positive patients (21, 8 and 2 respectively).[31-33] Combinations of immunotherapy and ALK inhibitors have been associated with significant toxicity and further development may be limited. From a biomarker perspective, there is a correlation between driver mutations and PDL1-positive status, but this does not appear to correlate with clinical benefit.

Brigatinib is seeking reimbursement approval for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor. The request has been made based on the interim analysis results of the ALTA-1L trial[1,2], an ongoing phase III randomized controlled trial (RCT) of brigatinib versus crizotinib.

Second-line

Ceritinib has demonstrated an ability to overcome resistance to crizotinib in the second line setting. ASCEND 5[34] was a phase III RCT that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC who had progressed on or who were intolerant to crizotinib and had prior platinum-based chemotherapy (N = 231). Patients were randomized (1:1) to receive ceritinib 750mg daily or chemotherapy. Those randomized to the chemotherapy group were treated with either docetaxel or pemetrexed per the investigator's choice. Patients with documented disease progression in the ceritinib group could

continue receiving ceritinib or discontinue treatment and enter the survival follow-up phase of the study. In contrast, patients who were randomized to the chemotherapy group were given the option to enter the extension phase, where they received treatment with ceritinib, or they could discontinue their assigned treatment and enter the survival follow-up phase. Treatment with ceritinib was associated with a statistically significant prolongation of PFS as compared to chemotherapy in patients with ALK-positive NSCLC (5.4 vs. 1.6 months; HR, 0.49; 95% CI, 0.36 – 0.67; P < 0.0001). The response rate was superior with ceritinib (45%) versus chemotherapy (7%). Overall survival was a key secondary endpoint measured from randomization to death due to any cause. The data presented thus far is immature, however, there was no difference in OS at the time of publication likely due to crossover (HR, 1.00; 95% CI, 0.67 – 1.49; *P* = 0.496). Ceritinib was recommended for reimbursement in March 2017 for treatment as monotherapy in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. Ceritinib is currently publicly funded for this patient population in most of the provinces.

Alectinib also demonstrated activity in the second line setting with the phase III trial, ALUR,[35] for patients with two previous systemic lines of therapy consisting of one platinum-based chemotherapy regimen and one line of crizotinib. Patients were randomized to receive either alectinib (600mg orally twice daily) or chemotherapy every three weeks consisting of pemetrexed or docetaxel. One hundred and seven patients were randomized (alectinib, N = 72; chemotherapy, N = 35) in 13 countries across Europe and Asia. The primary endpoint, median investigator-assessed PFS, was 9.6 months (95% CI, 6.9 – 12.2) with alectinib and 1.4 months (95% CI, 1.3 – 1.6) with chemotherapy (HR, 0.15; 95% CI, 0.08 – 0.29; *P* < 0.001). BIRC-assessed PFS was also significantly longer with alectinib (HR, 0.32; 95% CI, 0.17 – 0.59). Investigator-assessed ORR was 37.5% with alectinib versus 2.9% with chemotherapy. In patients with measurable baseline CNS disease, the objective response rate was significantly higher with alectinib (54.2%) versus chemotherapy (0%; P < 0.001). Alectinib was recommended for public reimbursement for monotherapy for the treatment of patients with ALK-positive, locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or are intolerant to crizotinib until loss of clinical benefit. For patients treated with crizotinib in the first line setting, the therapy of choice in the second-line setting is alectinib due to the excellent toxicity profile compared to ceritinib. Alectinib is currently funded in most provinces for this patient population.

Platinum doublet chemotherapy (particularly platinum combined with pemetrexed) is an additional option following treatment with an ALK inhibitor. Platinum pemetrexed chemotherapy appears to have activity in ALK-positive NSCLC that is similar to that seen in advanced NSCLC without ALK rearrangements.[36]

In 2018, brigatinib was reviewed by pERC for ALK-positive NSCLC patients who have progressed on or who were intolerant to an ALK inhibitor (crizotinib) but was not recommended for reimbursement. In 2019, lorlatinib was reviewed by pERC for ALK-positive patients who have progressed on crizotinib and at least one other ALK inhibitor, or patients who have progressed on ceritinib or alectinib, but was not recommended for reimbursement.

3 Summary of Patient Advocacy Group Input

One input was provided by Lung Cancer Canada (LCC) for the review of Brigatinib (Alunbrig) for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor. A questionnaire was conducted, and one patient was interviewed. The data from the survey was accessed between September to October 2020.

According to the patient input, the requested treatment is not currently available in Canada. Therefore, in order to find patients who had experience with the treatment under review, LCC outsourced input through environmental scans, surveys, patient and caregiver interviews and physician outreach. Two patients had experience with the drug under review. Their demographics can be found in Table 4. Additionally, LCC utilized input from patients who have taken brigatinib for the treatment of ALK-positive NSCLC in the second line. Seven respondent inputs were collected from previous submissions, one survey and environmental scanning. A total of 9 patients provided input for this submission.

Table 4: Demographics of Patients who had Experience with Brigatinib

Gender	Age	Year of Diagnosis	Location	Source of Input
Male	45	2019	USA	Interview
Female	32	2017	United Kingdom	Survey

Currently, there are a number of targeted therapies such as alectinib and crizotinib to treat patients with ALK-positive NSCLC. According to the input received, current therapies, allow patients to be functional and active, have a good QoL, live longer, and improve their prognosis and survival rates. Crizotinib was the first efficacious option for ALK-positive NSCLC. Many respondents on this treatment have reported being active and highly functioning. Reported side effects on crizotinib were nausea, vomiting, diarrhea, visual disturbances, edema and fatigue. Some patients did find the side effects intolerable. Alectinib is publicly covered as a first- and second-line treatment option. This treatment has presented better efficacy and lower toxicity compared to crizotinib. It has been found to be effective in treating patients with brain metastases, thus reducing or eliminating the need for whole brain radiation. It is generally very well tolerated with manageable side effects.

Patients with the ALK mutation commonly present with brain metastases at diagnosis; this has been observed in about 30% of patients and can limit their survival. Brain metastases can be quite debilitating, affecting patient QoL and resulting in a poorer prognosis. Crizotinib has a lower efficacy particularly with CNS involvement, however alectinib has been found to be effective in treating patients with brain metastases. While currently options exist to treat ALK positive NSCLC in the first line, there is an unmet need to provide treatments that are effective in treating brain involvement and delaying progression.

Improved outcomes expected from new therapies reported by patient respondents included being effective at treating CNS metastases, improved symptoms, prolonged survival, a good QoL, manageable side effects, longer lasting durable treatment and delayed progression of disease.

Two patient respondents spoke to their experiences with brigatinib as a first-line treatment. They commented on how brigatinib has controlled their cancer, reduced the size of their tumors and allowed them to live a productive and fulfilling life. Common side effects reported by respondents of the drug under review include fatigue, vomiting, diarrhea, constipation, abdominal pain and muscle and joint pain.

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

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Currently, there are a number of targeted therapies such as alectinib and crizotinib to treat patients with ALK-positive NSCLC. Current therapies, tailored to patient preferences have treated their disease while allowing patients to be functional and active, giving them a better QoL, allowing them to live longer, and improving their prognosis and survival rates. According to the patient input, for years, lung cancer patients have had limited options for long-term survival, however today many treatments have improved survival rates, and many patients are able to live and thrive.

As a result, ALK-positive lung cancer patients have come to expect a good QoL, they expect to live longer, to be able to tolerate the medication they are given and to have fewer, manageable side effects. Current treatments have given these patients better QoL. With alectinib, patients have also come to expect a certain amount of control over their brain metastasis.

One respondent; an 11-year ALK-positive, stage 4 lung cancer survivor, has been able to fulfill a healthy and happy life with targeted therapy. Another respondent, a 6-year survivor whose eldest son was 12 years old when they were diagnosed spoke to how years ago, they hoped to see their son reach grade 12 and attend University. This has been a possibility with their current treatment.

Patients with the ALK mutation commonly present with brain metastases at diagnosis, this has been observed in about 30% of patients and can limit their survival. Brain metastases can be quite debilitating, resulting in a poorer prognosis and reducing already low survival rates even further. While there currently exist options to treat ALK positive NSCLC in the first line, there is an unmet need to provide treatments that are effective in treating brain involvement and delaying progression. Having treatments that treat brain metastases would reduce the need for other treatments that can result in cognitive side effects further impacting a patient's QoL. Brain metastases have serious consequences and a poorer prognosis. While alectinib has been shown to have an effect on the brain, there is a significant need for additional treatment options.

One respondent spoke to how when they received a diagnosis one year ago, it came as a shock and was tough to digest. Finding out there was a treatment that could target this specific mutation and brain metastasis gave the patient hope for the future. The respondent was eager to get back to joining the work force despite their diagnosis. They were able to go back to work full time after starting treatment with brigatinib.

3.1.2 Patients' Experiences with Current Therapy

The current standard of treatment for ALK-positive NSCLC is alectinib and crizotinib. According to the patient respondents, both treatments extend life and allow patients to have a good QoL. They are oral medications that have shown to have manageable side effects and have improved patient outcomes. Many patient and caregiver respondents spoke to being able to fulfill more active lives because of these treatments. The patient group indicated that the *Faces of Lung Cancer* survey alone received input from 72 caregivers, and recent brigatinib submissions have received input from 4 caregivers.

According to the patient respondents, patients expect certain efficacies and livelihoods with treatments, and any new treatment option should be evaluated using the same criteria and expectations as the current options.

Crizotinib was the first efficacious option for ALK positive NSCLC. Many respondents on this treatment have reported being active and highly functioning. One respondent spoke to their treatment on crizotinib.

- *In six weeks, my tumour was half the size it was and in 12 weeks it was quarter of the size. I was symptom free and off oxygen. I was back to being myself. I looked so good that I was apologizing for looking so good!*

For patients with a CNS involvement at diagnosis, crizotinib may not provide adequate protection. Data have shown that since crizotinib is not able to cross the blood brain barrier, it is unable to effectively protect and treat CNS involvement and delay or prevent metastasis to the brain. Many patients and their physicians would prefer a treatment that would address any CNS involvement and reduce the need for other treatments such as radiation therapy that may result in cognitive deficits.

Respondents from previous submissions spoke to manageable side effects of crizotinib. Reported side effects were nausea, vomiting, diarrhea, visual disturbances, edema and fatigue. Some patients found the side effects intolerable. One patient said that crizotinib was challenging and affected their QoL. They were so nauseous that getting out of bed was difficult. Another patient had to discontinue crizotinib due to liver dysfunction.

Alectinib is the most commonly used treatment for ALK-positive NSCLC patients and is publicly covered as a first- and second-line treatment option. One respondent with experience with alectinib, who never expected that six years later they would be alive, is vibrant and living life. This treatment has presented better efficacy and lower toxicity compared to crizotinib. It has been found to be effective in treating patients with brain metastases, thus reducing or eliminating the need for whole brain radiation. It is generally very well tolerated with manageable side effects.

Both alectinib and crizotinib have allowed patients to live longer and experience greater QoL. Patient respondents have been able to remain independent, functional and physically active. ALK-positive patients expect and enjoy a good QoL on these treatment options.

3.1.3 Impact on Caregivers

Lung cancer affects not just those who are diagnosed, but also those caring for them. The diagnosis and treatment of lung cancer has a major impact on the life of the patient, and their caregivers who spend time providing care and support. The input received from caregivers is from previous sources of information such as interviews, environmental scans and surveys of lung cancer patient caregivers. As the treatment under review is not available in Canada, information was outsourced from previous submissions. Lung Cancer Canada noted there is no reason to expect differences in caregiver experiences compared to first line treatment as the same drug is being used. Caregivers experience a range of stressors, including changes in the family role and financial and occupational strain. The physical and emotional toll can leave caregivers feeling stressed, anxious and even depressed. In some cases, caregivers feel as much stress as their patients, which can affect their ability to fulfill their role at home and at work.

With many caregivers playing a central role in the management of patient care such as being involved in daily activities, medical care, and providing financial or emotional support, there is a need for more durable treatments which would help decrease the demand on the caregivers and allow patients to return to life. With additional treatment options that harbour more tolerable side effects, caregivers can continue working, and reduce the need to take medical leave to care for their loved ones. This will, in turn, reduce physical and financial burdens on the family.

For patients on targeted therapy, oral medications have more manageable side effects. Patient respondents were able to get out of bed, go for their appointments by themselves and go back to work, enabling caregivers to continue fulfilling their professional goals. Unlike chemotherapy or immunotherapy (IV treatments), where caregivers are required to help take their loved ones to appointments on top of managing other familial needs. To ensure the proper care of their loved ones, many caregivers take additional time off work resulting in decreased productivity, further leading to financial stress. Oral treatments allow caregivers to stay productive while simultaneously caring for their loved ones.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Patient respondents expect improved outcomes including being effective at treating CNS metastases, improved symptoms, prolonged survival, a good QoL, manageable side effects, longer lasting durable treatment and delayed progression of disease.

3.2.2 Patient Experiences to Date

Brigatinib is currently not available in Canada, therefore LCC gathered experience from two patients outside of Canada. One in the United States and one in the United Kingdom. Both patients spoke to their experiences with brigatinib as a first line treatment. The patients noted that brigatinib is an ALK inhibitor that is effective in treating systemic and CNS involvement. It has the potential to prolong survival and improve patient outcomes. The patient respondents noted that brigatinib offers ALK-positive patients similar if not better outcomes compared to the current standards. Further, they noted that the treatment under review would provide an additional viable option for ALK-positive patients who may be unable to tolerate the current options.

One patient respondent spoke to how brigatinib has controlled their cancer and is a durable form of treatment. Following a craniotomy to remove a tumor in their cerebellum, the patient was treated with brigatinib. Within a month of being on the treatment under review, the tumor in the patients left lung had reduced from 2.7cm to 1.4cm, and the tumors on the right side of the lung had disappeared. The remaining residual spots left in their brain post-surgery had also disappeared. The patient currently has no evidence of disease (NED). They have been taking brigatinib for a year, and they are currently active, spend time with family and friends, and are able to work full time.

The second patient respondent has been on brigatinib for 45 months in duration. Since starting brigatinib, the patient reported a vast reduction in the size of their tumor. Unfortunately, while on brigatinib the patient developed brain metastases at 40 months. The patient credits their current health and good QoL to brigatinib and believes the progression of their brain metastases would have been quicker without the drug under review.

Common side effects reported by respondents of brigatinib include fatigue, vomiting, diarrhea, constipation, abdominal pain and muscle and joint pain. One of the patient respondents reported that they had no side effects from treatment and returned to work in 14 days after surgery. The other respondent indicated that they experienced diarrhea and joint pain with their treatment, however their side effects were manageable. While they are currently not working, they stated that their treatment has allowed them to continue pursuing important hobbies.

Seven patients who had experience with brigatinib in the second line reported mild side effects with a reduction in disease progression. One patient spoke to their experience with brigatinib following an MRI showing multiple nodules in their brain.

- *Scans show everything is shrinking and disappearing, it is doing its job.*

Side effects reported by this patient were diarrhea and constipation with some mild pain issues, however exercising helped with the aches and pains. The patient's scans showed an 80% shrinkage in the lung tumor as well as favorable activity in the lymph nodes and bone metastases. By the four-week mark, the patient's brain metastases were all gone. Other patient respondents have reported favorable results with brigatinib such as, their brain tumor disappearing and remaining stable, and the disappearance of brain metastases.

Many patients reported that their side effects were tolerable; one patient specifically described how their experience with brigatinib was much easier than their experience with crizotinib which caused significant GI issues.

Respondents described how brigatinib has improved their (and their loved ones) QoL and has allowed them to enjoy life's activities. The following respondent quotes explain patients QoL on brigatinib:

- *While he does experience some side effects with brigatinib, it does not stop him from doing what he wants. We travel with no problems.*
- *I may have cancer, but cancer does not have me.*

Lung Cancer Canada noted that the experiences gathered show that brigatinib is clinically beneficial and effective for the treatment of ALK-positive NSCLC. This form of therapy is effective, durable, compares well with the current treatment standard and addresses an unmet need. The patient input states that patients are willing to tolerate a high pill burden if it will save their lives, however, brigatinib is a once a day, low dose pill will that allow patients to have a better QoL.

Lung Cancer Canada noted there is no reason to expect differences in patient experiences compared to first line treatment as the same drug is being used. Furthermore, the patient input noted that experience in the second line is significant as this group of patients are more experienced with previous treatments and may be harder to treat. Additionally, according to LCC, the side effects of brigatinib are similar to alectinib and crizotinib based on patient experiences.

3.3 Companion Diagnostic Testing

The patient input from LCC stated that ALK-positive testing is currently standard practice in many provinces across the country.

3.4 Additional Information

There has been remarkable progress in the treatment of lung cancer in the last decade. ALK-positive NSCLC has been fortunate to have a number of available treatment options. Alectinib and crizotinib are currently the first line options in this landscape, however data from the Phase 3 (gold standard) ALTA 1L trial showed that brigatinib demonstrated superior efficacy, especially among those with brain metastases particularly at diagnosis and was more effective than crizotinib. This is an important factor to consider when determining a treatment option that can treat and control a disease condition with possible CNS involvement. ALK-positive patients need more options for treatments than are currently available.

The patient group stated that they believe there is no reason why brigatinib should not be a first-line treatment option for this group of patients. This treatment is a beneficial form of therapy for first-line patients and should be considered. The patient group also believes the inclusion of another option onto the public formulary will help create downward pricing pressure and drive down costs in our publicly funded healthcare system. Funding this treatment would contribute to responsible and resourceful use of tax dollars.

The patient group indicated that brigatinib is a treatment that provides patients with clinical benefits and expectations that meet the criteria disputed by pERC in previous submissions. They wanted to stress that it would be unjust not to provide patients diagnosed with NSCLC, the best chance possible at living a good QoL. Lung Cancer Canada believes brigatinib will address an unmet need and provide an alternate option of treatment for patients.

4 Summary of Provincial Advisory Group (PAG) Input

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

Overall Summary

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

Overall Summary

Input was obtained from nine provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could be impact implementation of brigatinib in the treatment of non-small cell lung cancer (NSCLC):

Clinical factors:
- Time-limited need for patients receiving treatment with either crizotinib or alectinib
- Sequencing and priority of treatments

Economic factors:
- None

Please see below for more details.

4.1 Currently Funded Treatments

Currently, the standard first line therapy for patients with ALK-positive locally advanced or metastatic non-small NSCLC who were previously untreated with an ALK inhibitor is crizotinib or alectinib.

PAG noted that the ALTA-1L trial compared brigatinib with crizotinib. PAG is seeking an additional comparison of brigatinib with alectinib.

4.2 Eligible Patient Population

The reimbursement request is for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor.

In view of the characteristics of the included patient population and exclusion criteria in the ALTA-1L trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with brigatinib:

- patients that previously received more than one systemic anticancer therapy regimen for advanced disease or chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days before the first dose of brigatinib
- patients with ECOG PS>2
- patients with symptomatic CNS metastases

PAG is seeking advice on a time-limited need to cover patients who were receiving treatment with crizotinib or alectinib and may be better candidates for treatment with brigatinib.

PAG is concerned by the potential indication creep on the following scenarios: use in second line or later settings, use in neoadjuvant or adjuvant treatment of resectable NSCLC.

4.3 Implementation Factors

The recommended dose for brigatinib is 90 mg orally once daily for the first 7 days. If 90 mg is tolerated during the first 7 days, the dose is increased to 180 mg orally once daily. Available strengths of brigatinib include tablets of 30mg, 90 mg and 180 mg.

PAG noted that brigatinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler. Brigatinib is supplied in a one-month initiation pack. 90 mg and 180 mg tablets are available in aclar/foil blister 28 film-coated tablets (4 cards of 7 tablets). PAG stated that with lead in dosing, this may be confusing for patients. Furthermore, multiple strengths of brigatinib is an enabler of implementation. PAG noted that 90 mg and 180 mg tablet strengths are the same price regardless of strength. This flat pricing structure would be a barrier as there would be added costs for dose modifications. There is also concern with the potential for drug wastage for patients starting on 90 mg for 7 days and then if tolerated, increasing this dose to l80 mg. This is a potential challenge among ambulatory patients.

PAG is seeking clarity on treatment until “disease progression” and “unacceptable toxicity.”

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy and sequencing of brigatinib including the scenarios below:

- What treatment options would be available to patients who progressed on brigatinib? PAG noted that alectinib and ceritinib are indicated for patients that progressed on or were intolerant to crizotinib
- What treatment options would be available to patients who discontinued brigatinib in the case of toxicity?

4.5 Companion Diagnostic Testing

ALK mutation testing is being conducted at diagnosis to determine appropriate treatment.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered joint clinician inputs were provided on behalf of three clinicians from Ontario Health Cancer Care Ontario (CCO) and 13 clinicians from Lung Cancer Canada (LCC) for the review of brigatinib (Alunbrig) indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who were previously untreated with an ALK inhibitor.

Lung Cancer Canada stated that of the current treatments available, crizotinib and ceritinib are no longer considered appropriate comparators for the drug under review. Both clinician groups indicated that the most appropriate comparator in the first-line setting is alectinib.

Both clinician groups stated that they would prescribe brigatinib to patients with advanced ALK-positive NSCLC in the first line setting. Clinicians from CCO, stated that because alectinib is already used in the first line, brigatinib would be an additional option, and there is not an unmet need. In contrast, clinicians from LCC indicated that there is a significant unmet need for additional ALK-targeting agents in all lines of therapy, including first line. In the event that alectinib is not available, it would be beneficial to have another option.

Both clinician groups had experience using brigatinib and described how they would use brigatinib in the first line setting as an alternative to alectinib. Clinicians from LCC stated that given the prevalent and established use of alectinib in the first-line setting, and its dominance over early generation ALK TKIs such as crizotinib and ceritinib, brigatinib will likely be used in the first-line setting under specific circumstances when an alternative is preferred or required (i.e., toxicity by alectinib). The selection of brigatinib as a first line therapy may be preferred due to its efficacy in treating brain metastases at baseline. Brigatinib has higher Grade 3+ toxicities than alectinib. The difference is mostly related to deranged biochemical parameters (CK, liver enzyme, amylase elevations) of unknown significance, which can lead to higher rates of dose interruptions and dose reductions. Brigatinib has similar low toxicity-related treatment discontinuation rates as alectinib. According to clinicians, both drugs are well tolerated by patients. Both clinician groups stated that ALK testing has been standardized in Canada and as a result, jurisdictions across Canada have uniformly adopted its use in routine lung biomarker testing.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

Lung Cancer Canada stated that of the current treatments available, crizotinib and ceritinib are no longer considered appropriate comparators for brigatinib. Currently, crizotinib is not used as first-line treatment whenever alectinib is available because of its inferiority in PFS and poorer primary and secondary control of brain metastases (ALEX trial). Ceritinib's greater intolerability, particularly gastrointestinal toxicity, even at its 450mg daily dosing given with food, has led to clinicians avoiding its use since the ALEX trial data was released. Both clinician groups indicated that the most appropriate comparator in the first-line setting is alectinib. According to LCC clinician input, crizotinib is funded in all provinces and ceritinib and alectinib are funded in most provinces and currently under consideration in others.

5.2 Eligible Patient Population

Both clinician groups stated that they would prescribe brigatinib in patients with advanced ALK-positive NSCLC in the first line setting. Clinicians from CCO, stated that because alectinib is already used in the first line, brigatinib would be an additional option, and there is not an unmet need. In contrast, clinicians from LCC indicated that there is a significant unmet need for additional ALK-targeting agents in all lines of therapy, including first line. CCO clinicians stated that brigatinib is a superior treatment to crizotinib. In the event that alectinib is not available, or has supply chain issues, it is beneficial to have another option available.

While different from the specific population in the funding request, clinicians from CCO stated they would like to be able to use brigatinib in patients who have progressed on alectinib but have not taken crizotinib.

Clinicians at LCC indicated that the inclusion and exclusion criteria of ALTA-1L trial is widely applicable to clinical practice. Between 30-40% (ALTA-1L; ALEX trial data) of patients present with brain metastases prior to ALK inhibitor exposure, and thus inclusion of these patients is relevant to clinical practice. Although reflexive testing of ALK is commonplace in Canada (especially given low-cost ALK immunohistochemistry testing), a small subset of patients may have chemotherapy started prior to obtaining ALK status. Other patients may have failed platinum-based chemotherapy, either as an adjuvant therapy or very rapidly as part of definitive chemo-radiation, therefore their chemotherapy would have been considered as first-line therapy for metastatic disease in the original trial. This broad eligibility helps with application in clinical practice.

While clinicians at LCC agreed that there were no important subgroups in the trial that should be identified, they stated that there are subgroups of patients beyond the study population of ALTA-1L that would benefit from the new treatment that will be covered by the requested Health Canada indication. This information, however, is not specific to the eligible patient population or population under review. There is real world data showing benefit of brigatinib after other ALK TKIs, and in particular, after alectinib. Examples are as follows;

1. An early report found only 3 of 18 patients had confirmed objective responses to brigatinib after alectinib, while another 9 had developed stable disease; median PFS was 4.4 months. However, this case series does not entirely fit with the current circumstances, as only 3 of the patients had received alectinib first-line, and the sample size was small. (JJ Lin et al; Brigatinib in Patients With Alectinib-Refractory ALK-Positive NSCLC. J Thorac Oncol 2018 Oct;13(10):1530-1538).

2. In a much larger report, another real-world study suggests substantial clinical benefit of brigatinib after crizotinib, ceritinib, alectinib, and lorlatinib with times-to-treatment discontinuation of 10.0, 8.7, 10.3 and 7.5 months, respectively. While only 8 patients had received first-line alectinib, 79 patients did have alectinib as its last line prior to brigatinib exposure (HM Lin et al. Real-world treatment duration in ALK-positive non-small-cell lung cancer patients receiving brigatinib through the early access program; Future Medicine 2020 (27 Apr); 16(15)).

3. The ATOMIC brigatinib study (NCT02706626) reported at a 40 percent response rate in 20 patients treated with brigatinib after first-line treatment with another next-gen ALK inhibitor (that was mainly alectinib). With median follow-up of 6.7 months (11 PFS events), the median PFS was 6.4 months (95% CI: 4.6 to NE). Due to COVID-19 interruptions, this trial is closing in October 2020 (ASCO 2019 abstract 9027).

4. A French retrospective study of 104 patients demonstrated a 50 percent response rate in patients treated with brigatinib after two previous lines of ALK inhibitor therapy. Due to many patients receiving crizotinib and ceritinib before alectinib, results for the post-alectinib subgroup are best mirrored in those with 3-4 and >4 lines of treatment before brigatinib; PFS was 10.4 (5.9-13.9) and 3.8 (0.8-7.4) months, respectively. Using sequencing of TKIs with a median of 4 lines of therapy (including brigatinib), the median OS from the diagnosis of NSCLC was 75.3 (38.2-174.6) months. (R Descourt et al; Brigatinib in patients with ALK-positive advanced non-small-cell lung cancer pretreated with sequential ALK inhibitors: A multicentric real-world study (BRIGALK study). Lung Cancer 2019 Oct; 136:109-114.)

From this data, there is evidence of the activity of brigatinib post-alectinib, which aligns with what clinicians at LCC have seen in clinical practice. There is also a critical unmet need for ALK TKIs for sequential use after first line therapy with a second or next-generation TKIs, and this is substantiated by the real-world data from the French retrospective study: median OS of 75 months (6+ years) is unheard of before the era of sequencing multiple monotherapy ALK TKIs. In general, following the failure of these TKIs are standard chemotherapy and/or immunotherapy options considered in most Canadian practice settings.

From a Canadian dataset of 76 ALK-positive patients (and 499 data points) treated with ALK TKIs at Princess Margaret Cancer Centre, the longitudinal on-treatment health utility scores of later generation ALK inhibitors (specifically alectinib, brigatinib, and lorlatinib) is between 0.8-0.9 over time, when the disease is clinically/radiologically controlled; median OS in this group of patients was 5.8 years (4.9-NE) (Tse et al. Longitudinal health utilities, symptoms and toxicities in Anaplastic Lymphoma Kinase (ALK) rearranged lung cancer patients treated with tyrosine kinase inhibitors: A prospective, real world assessment. Current Oncology, in press, 2020).

Due to the complexity and samples sizes required, it is unfeasible to perform a clinical trial that will randomize to sequencing three or more ALK-TKIs (alectinib, brigatinib, lorlatinib), one after another. The best option may be a rational approach based on mutational

data at disease progression such as suggested by the ALK MASTER protocol (NCT03737994), which is currently expected to yield data in 2025. LCC clinicians stated that patients need a pragmatic approach now to manage their advanced/metastatic ALK-rearranged cancers: real-world evidence has demonstrated that the paradigm is changing in the management of ALK patients globally to focus on sequencing of monotherapy ALK-TKI drugs, which appears to be a pragmatic way to prolong life while preserving quality-of life, based on multiple sources of real-world and some trial data (NCT01970865).

5.3 Relevance to Clinical Practice

Both clinician groups had experience using brigatinib and described how they would use brigatinib in the first line setting as an alternative to alectinib.

Clinicians from LCC stated that given the prevalent and established use of alectinib in the first-line setting, and its dominance over early generation ALK TKIs such as crizotinib and ceritinib, brigatinib will likely be used in the first-line setting under specific circumstances when an alternative is preferred or required (i.e., toxicity by alectinib).

The selection of brigatinib as a first line therapy may be preferred due to its efficacy in the treating brain metastases at baseline. Brigatinib has higher Grade 3+ toxicities than alectinib. The difference is mostly related to deranged biochemical parameters (CK, liver enzyme, amylase elevations) of unknown significance, which can lead to higher rates of dose interruptions and dose reductions. Brigatinib has similar low toxicity-related treatment discontinuation rates as alectinib. Clinicians felt that both drugs are well tolerated by patients.

Clinicians at LCC indicated that the one clear contraindication to using brigatinib is in the setting of baseline hypoxia and/or significant baseline dyspnea, given the rare complication of an early onset pulmonary event. This has not been observed with alectinib.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The only funded option in Ontario for previously untreated ALK-positive NSCLC is alectinib first line, or post crizotinib. Sequencing of treatments for patients who progress on alectinib first line, or additionally for patients who progress on brigatinib first line is unclear.

Clinicians at LCC identified that in addition to what was highlighted in previous sections, it is predicted that brigatinib will likely be given either as first-line therapy, followed by other second/next generation ALK TKIs, or as second or subsequent line therapy, following alectinib. In clinical practice, brigatinib could replace alectinib in the first line setting based on ALTA-1L. Alternatively, it could be used as an agent for unmet need after failure of alectinib, based on the real-world evidence shown above, and based on the requested indication.

5.4.1 Implementation Question: If brigatinib is reimbursed, is there a preference for brigatinib or alectinib in the first line setting? What circumstances would first line brigatinib be preferred over first line alectinib?

Clinicians at CCO stated that they would most likely choose alectinib for patients with liver disease or renal dysfunction. Any use of brigatinib will come at the expense of alectinib. It is expected to be relatively neutral in terms of cost if brigatinib and alectinib are similarly priced.

Clinicians at LCC indicated that in general, alectinib has become the standard first-line therapy for ALK-naïve advanced/metastatic NSCLC patients. It is well tolerated and efficacious. Thus, there would have to be specific reasons to consider brigatinib as an alternative in the first-line setting. Examples are as follows:

1. Data on the overall BIRC-assessed PFS of patients who have brain metastases at baseline suggest that the subpopulation of patients with baseline brain metastases derive greater benefit from brigatinib than from crizotinib. It would be this population where there may be preference of brigatinib over alectinib. A recent NMA supports this view (K Ando et al; Brigatinib and Alectinib for ALK Rearrangement-Positive Advanced Non-Small Cell Lung Cancer With or Without Central Nervous System Metastasis: A Systematic Review and Network Meta-Analysis Cancers (Basel) 2020 Apr 10;12(4):942). Control of brain metastasis is an incredibly important factor in patients' quality-of-life. Since typical ALK-rearranged patients

are younger and healthier, and often in their working years, the impact of brain metastases on these patients can be devastating to their lifestyle and their ability to work and function.

2. Brigatinib and alectinib have different toxicity profiles. There would be preference for alectinib in patients who have baseline dyspnea or hypoxia, in order to avoid the potential for early onset pulmonary events, and in patients with poorly controlled hypertension (Camidge et al, Brigatinib versus crizotinib in advanced ALK-inhibitor-Naïve ALK-positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial; J Clin Oncol (in press)). Alternatively, patients and physicians may prefer to use brigatinib when there are patient concerns about the development of weight gain, peripheral edema, myalgia, constipation, and blurry vision. Although most of these toxicities are Grade 1 or 2, even low-grade toxicities, when occurring continuously over years, can lead to substantial decreases in quality-of-life. (Camidge DR et al, Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study.J Thorac Oncol. 2019 Jul;14(7):1233-1243).

3. Both brigatinib and alectinib have low but finite rates of discontinuation due to toxicity, 13% in ALTA-1L and 11% in ALEX respectively; thus, an equally effective alternative should be available when toxicity causes discontinuation of the first drug.

4. There is real world data to suggest potential clinical benefit of brigatinib after alectinib (see above) and alectinib after brigatinib (see below). This data consists mostly of case reports and case series; the sizes of the case series supporting the potential clinical use of brigatinib after alectinib is greater than alectinib after use of brigatinib, but in both circumstances the data are based on real world data and case series.

5. If there are issues related to patient compliance, brigatinib is a once daily single pill. Alectinib is twice daily, and typically a total of eight pills in one day. In this instance, brigatinib would be preferred.

5.4.1 Implementation Question: What evidence is there to inform the sequencing of alectinib or other ALK TKIs after first line brigatinib?

Clinicians at LCC stated that there is little data published in the area of alectinib use after brigatinib. Recently, there was a published report of three cases whereby alectinib partial responses were observed, where all three patients were still on the drugs at the time of publication (with follow-up times of at 18 months, 6 months, and 5 months, respectively, based on manuscript submission dates) (*MJ Hochmair, et al; Alectinib following brigatinib, Anti-Cancer Drugs: August 27, 2020 - Volume Publish Ahead of Print - Issue - doi: 10.1097/CAD.0000000000000989*).

Clinicians at CCO stated that there is evidence from a phase II study showing activity for lorlatinib for patients who have progressed on second-generation ALK inhibitors like alectinib or brigatinib with a response rate of about 40% (better than chemotherapy).

Similarly, LCC clinicians stated that there is slightly more data on lorlatinib being active after use of a second-generation ALK inhibitor. In a phase II trial of patients with *ALK*- or *ROS1*-positive advanced or metastatic NSCLC, lorlatinib induced a response in 69.5%. In patients who had previously received crizotinib, the ORR was 69.5%. In those with ≥1 ALK inhibitors, the ORR was 47%. The estimated median duration of response was 12.5 months. However, few of the patients had received brigatinib in a prior line, in comparison to crizotinib, ceritinib, and alectinib. (*BJ Solomon, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study.Lancet. 2018;19(12):1654-1667*).

Further, there is anecdotal evidence that after intracranial-only failure of second generation ALK TKI such as brigatinib, patients can benefit from lorlatinib (*I Dagogo-Jack, et al. A phase II study of lorlatinib in patients (pts) with ALK-positive (ALK+) lung cancer with brain-only progression. J Clin Oncol 38, no. 15_suppl (May 20, 2020) 9595-9595; MR Sakamoto; Lorlatinib Salvages CNS Relapse in an ALK-Positive Non–Small-Cell Lung Cancer Patient Previously Treated With Crizotinib and High-Dose Brigatinib. Clin Lung Cancer 2019 (Mar 1); 20 (2) E133-E136*).

Funding for lorlatinib in second and subsequent lines of therapy has not been recommended by pERC, and thus this option is currently not available through public access.

In summary, clinician inputs indicate that there is limited real world data on sequencing of drugs after brigatinib, though there is anecdotal evidence of potential benefit from either alectinib or lorlatinib.

5.5 Companion Diagnostic Testing

Both clinician groups stated that ALK testing has been standardized in Canada. LCC clinicians identified that ALK testing involves immunohistochemical staining first (Cutz et al, Canadian anaplastic lymphoma kinase study: a model for multicenter standardization and optimization of ALK testing in lung cancer; J Thorac Oncol 2014 Sep;9(9):1255-63). The immunohistochemistry test takes a few days to complete and report. This immunohistochemical test is inexpensive; as a result, jurisdictions across Canada have uniformly adopted its use in routine lung biomarker testing.

Across Canada, the majority of centres are performing reflexive ALK rearrangement testing in advanced/metastatic lung cancer; delays may occur under several common scenarios such as: (i) centres not performing the test have to send the slides to a central laboratory for testing, which may delay reporting; (ii) fewer than 5% of tests will be considered indeterminate on staining that would require FISH confirmation; (iii) some centres report ALK rearrangements alongside other lung biomarkers, and some of these other molecular tests take longer to complete and report. None of these potential reasons for delay should impact the management of patients.

5.6 Implementation Questions

Refer to implementation questions in respective sections above.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

To evaluate the efficacy and safety of brigatinib as monotherapy for the first-line treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC.

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. A summary and critical appraisal of a sponsor-submitted indirect treatment comparison (ITC) comparing brigatinib to alectinib and ceritinib for ALK-positive NSCLC are provided in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 5 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 5: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs. In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of brigatinib for ALK-positive NSCLC will be included.	Previously untreated adult patients (aged ≥18 years) with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC. Subgroups: • CNS metastases at baseline (Yes vs. No)	Brigatinib monotherapy	Crizotinib Alectinib	Efficacy: • **PFS** • **OS** • ORR • DCR • **DOR** • **CNS ORR** • CNS DOR • **Time to CNS progression** Safety: • **AEs** • SAEs • WDAEs Patient-reported outcomes/ **HRQoL**

AE = adverse events; ALK = anaplastic lymphoma kinase; CNS = central nervous system; DCR = disease control rate; DOR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS= overall survival; HRQoL=health-related quality of life; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events

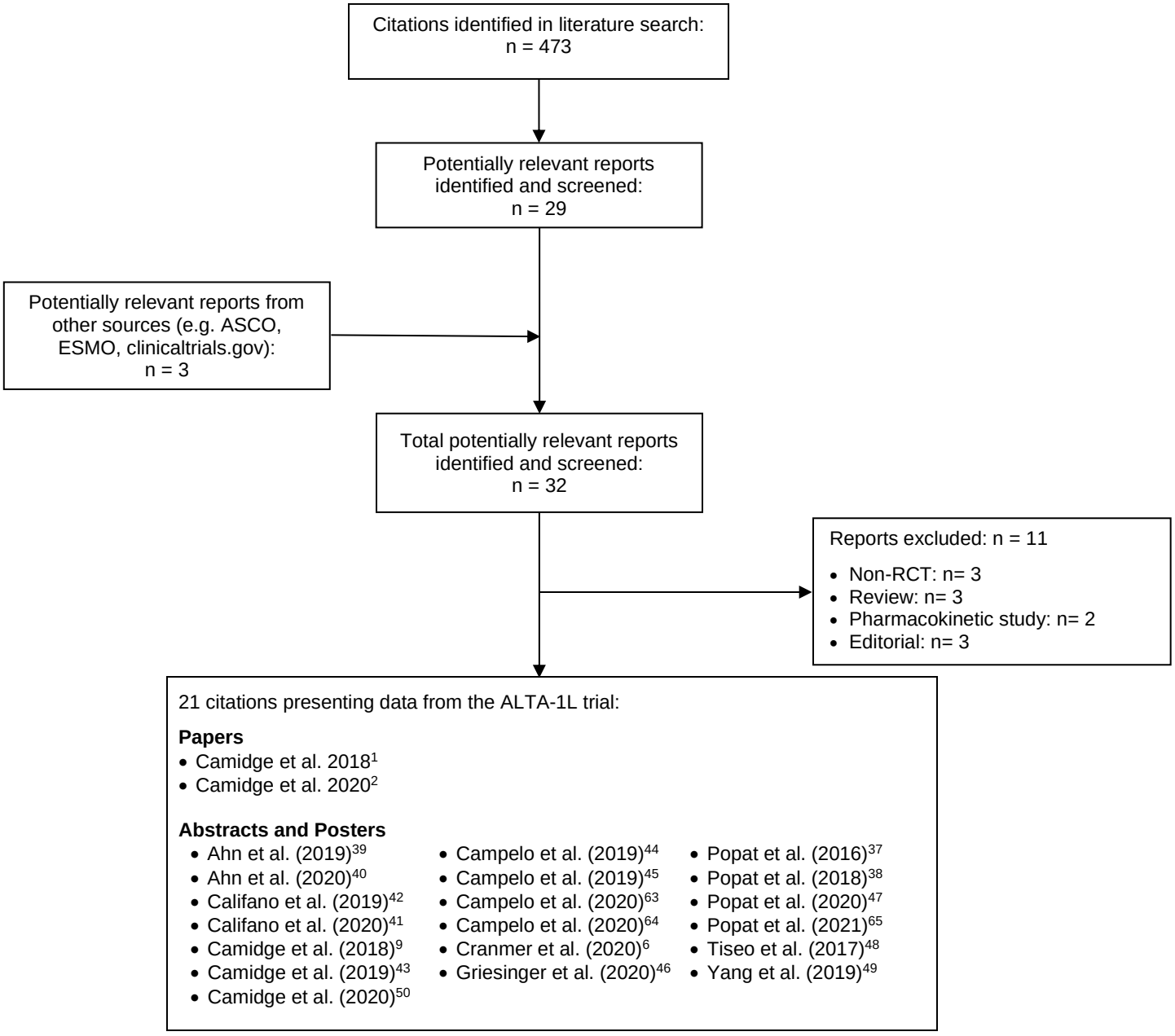
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 32 potentially relevant reports identified, 21 citations presenting data from one trial were included in the pCODR systematic review[1,2,9,37-51] and 14 citations were excluded. Reports were excluded because they were non-RCTs[52-54], reviews[55-57], pharmacokinetic studies[58,59], and editorials.[60-62]

Figure 1: Flow Diagram for Study Selection



Reports identified from other sources
• pCODR Submission[3,66] • EMA Report[7]

Note: Additional data related to the ALTA-1L trial were also obtained through requests to the Sponsor by CADTH.[3,66]

6.3.2 Summary of Included Studies

One RCT meeting the selection criteria was identified through the systematic literature review: the ALTA-1L trial (N = 275).

6.3.2.1 Detailed Trial Characteristics

The summary of the trial and select quality characteristics are presented in Table 6 and Table 7.

Table 6: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study ALTA-1L Trial[1] (NCT02737501) **Characteristics** Phase III, open-label, randomized trial, 1:1 ratio Randomized N = 275 Treated N = 273 **Number of Centres and Countries** 124 centres in 20 countries were engaged to participate in the trial.[1] Patients were randomized at 92 centres in 19 countries.[3] **Patient Enrolment Dates** April 2016 to August 2017 **Data Cut-off** First Interim Analysis Data Cut-off Date[1]: February 19, 2018 Second Interim Analysis Data Cut-off Date[2]: June 28, 2019 **Final Analysis Date** Trial is ongoing. A final analysis[e] is planned for June 2021[66] **Funding** Ariad Pharmaceuticals	Key Inclusion Criteria: • Age ≥18 years old • Histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for definitive multimodality therapy) or stage IV NSCLC • Documented ALK rearrangement by a local laboratory test[a] • Sufficient tumor tissue for central analysis • At least 1 measurable lesion per RECIST version 1.1 at baseline • Adequate hepatic, renal, and bone marrow function[b] • ECOG PS ≤ 2 Key Exclusion Criteria: • Previous treatment with an investigational anticancer agent for NSCLC • Previous treatment with a TKI • >1 regimen of systemic anticancer therapy for locally advanced or metastatic disease • Chemotherapy or radiation therapy within 14 days of first dose of study drug • Symptomatic CNS metastases (CNS metastasis allowed if asymptomatic;	Brigatinib 180 mg orally once daily after a 7-day lead-in period of 90 mg orally once daily *versus* Crizotinib 250 mg orally twice daily Until PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion[d] is met.	Primary: • PFS by BIRC Secondary: • ORR by BIRC • Intracranial ORR by BIRC • Intracranial PFS by BIRC • OS • DOR by BIRC • TTR by BIRC • DCR by BIRC • Safety and tolerability • Patient reported symptoms and HRQoL (EORTC QLQ-C30 and EORTC QLQ-LC13) Exploratory: • Confirmed ORR by BIRC for brigatinib in patients who crossover from crizotinib • PFS by BIRC for brigatinib in

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	leptomeningeal disease and without spinal cord compression allowed) • Pregnancy • Significant, uncontrolled, or active CVD[c] • Uncontrolled hypertension • Pulmonary interstitial disease or pneumonitis • GI disorder affecting absorption of oral medications		patients who crossover from crizotinib • Correlation of brigatinib PK with safety and efficacy • Molecular determinants of safety and efficacy for brigatinib and crizotinib

ALK = anaplastic lymphoma kinase; BIRC = blinded independent review committee; CNS = central nervous system; CVD = cardiovascular disease; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ= European Organization for Research and Treatment of Cancer quality of life questionnaire; GI = gastrointestinal; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria In Solid Tumors; TTR = time to response; TKI = tyrosine kinase inhibitor

Notes:
[a] Local laboratory tests acceptable for documenting ALK reengagement prior to randomization included the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) probe kit or the Ventana ALK (D5F3) CDx assay.
[b] Adequate organ function defined as: ALT/AST ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present; Total serum bilirubin ≤1.5 × ULN (<3.0×ULN for patients with Gilbert syndrome); Serum creatinine ≤1.5 × ULN; Serum lipase/amylase ≤1.5 × ULN; Absolute neutrophil count (ANC) ≥1.5 × 109/L; Platelet count ≥75 × 109/L; Hemoglobin ≥10 g/dL.
[c] Significant, uncontrolled, or active CVD included but not restricted to myocardial infarction, unstable angina, congestive heart failure, cerebrovascular accident, or transient ischemic attack within 6 months, clinically significant atrial arrhythmia.
[d] Discontinuation criteria included: entry into another clinical study, start of a new anticancer therapy, significant deviation from the protocol or eligibility criteria, non-compliance with study procedures, pregnancy.
[e] The final analysis is planned as a landmark analysis including OS, PFS, and safety/tolerability.[66]

Table 7: Select quality characteristics of included studies

Study	ALTA-1L Trial
Treatment vs. Comparator	Brigatinib vs. Crizotinib
Primary outcome	PFS by BIRC
Required sample size	270 participants were required to be included in the study. 198 events (progression or death) were required to provide 90% power to detect a 6-month improvement in PFS [hazard ratio (HR), 0.625], assuming a median PFS of 10 month in the crizotinib group, and using a two-side log-rank test with significance level of 0.0044 at the final analysis (adjusting for the two prespecified interim analyses to control the overall α level at 0.05).[1,3]
Sample size	275
Randomization method	Randomization was stratified by presence of brain metastases at baseline and previous chemotherapy for locally advanced or metastatic disease.
Allocation concealment	A central BIRC evaluated all images for progressive disease.
Blinding	Open-label trial.
ITT analysis	Yes

Final analysis	No. The trial is ongoing, and the final analysis is expected to be completed in June 2021 as a landmark analysis for PFS and OS and safety/torability.[66] Two planned interim analyses have been completed.
Early termination	No
Ethics approval	Yes

BIRC = blinded independent review committee; CNS = central nervous system, HR = hazard ratio, PFS = progression free survival

a) Trials

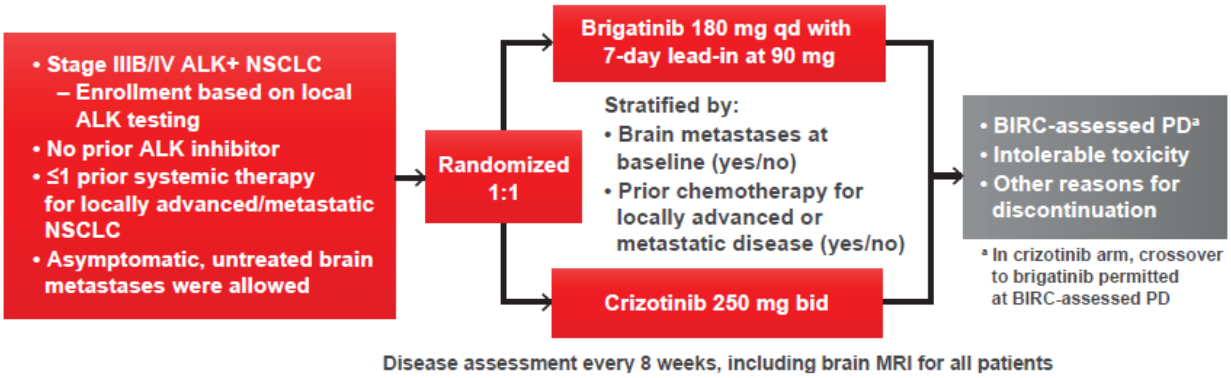
Trial Design

The ALTA-1L trial is an ongoing, open-label, multi-centre, active-controlled, randomized phase III trial of brigatinib compared to crizotinib in patients with advanced ALK-positive NSCLC who had not previously received an ALK inhibitor.[1] The ALTA-1L trial is an international trial that enrolled 275 patients from 92 sites in 19 countries. Most patients were from Europe and Asia. Patient enrolment took place between April 2016 and August 2017.[1] The trial was funded by Ariad Pharmaceuticals.[1] The trial sponsor was involved in all aspects of trial conduct, including the design, data analysis and interpretation, and preparation of the trial publication.[1]

Patients were included in the trial if they met the following key criteria[1]: adults with stage IIIB/IV ALK-positive NSCLC, at least one measurable lesion according to RECIST version 1.1 criteria, previously untreated with an ALK inhibitor, received ≤ 1 systemic chemotherapy regimen, and had an ECOG performance status ≤ 2. Patients were randomized based on the results of a local laboratory ALK test, which was later confirmed by central lab testing. Brain metastases at baseline were allowed if they were asymptomatic. Patients who had previous treatment with an investigational anticancer agent, a tyrosine kinase inhibitor (TKI), or more than one regimen of systemic anticancer therapy; chemotherapy or radiation therapy within 14 days of the first dose of study drug; significant, active, or uncontrolled cardiovascular disease; or a gastrointestinal disorder affecting oral absorption of drugs were excluded. Further details on the inclusion and exclusion criteria are provided in Table 6.

Patients were randomized in a 1:1 ratio to the brigatinib or crizotinib treatment groups. Patients were stratified according to the presence of brain metastases at baseline (Yes vs. No) and prior chemotherapy for locally advanced or metastatic disease (Yes vs. No), which was defined as completion of at least one full cycle of chemotherapy. To assess disease status, all patients underwent imaging at baseline, every 8 weeks through cycle 14 (28 days per cycle), and then every 12 weeks until the end of treatment. Two BIRCs performed disease assessments: one BIRC for all systemic disease according to RECIST version 1.1[67], and one BIRC exclusively for intracranial CNS outcomes according to modified RECIST criteria.[1] Treatment crossover from the crizotinib group to brigatinib was permitted at the investigator's discretion if the patient experienced disease progression as determined by the BIRC. The study design is illustrated in Figure 2.

Figure 2: ALTA-1L Trial Design



ALK = anaplastic lymphoma kinase; BID = twice daily; BIRC = blinded independent review committee; NSCLC = non-small cell lung cancer; PD = progressive disease

Source: Popat et al. Poster, European Society for Medical Oncology Virtual Congress, 2020[68]

Statistical Analysis

Outcomes: The primary outcome of the ALTA-1L trial was PFS as assessed by BIRC in the ITT population.[1] Key secondary outcomes were confirmed ORR by BIRC, intracranial ORR by BIRC, intracranial PFS by BIRC, and OS. Additional secondary outcomes included DOR, change from baseline scores in GHS/QOL assessed by the EORTC QLQ-C30 (version 3.0), time-to-deterioration in dyspnea assessed with the EORTC lung cancer-specific module (QLQ-LC13, version 3.0)[1] , and safety and tolerability.

Progression-free survival was calculated as the time from the day of randomization until the day of the first PFS event. It is censored for participants who have not had a PFS event. A PFS event was defined as death or disease progression by RECIST version 1.1, whichever occurs first. Overall survival was defined as the time from the date of randomization until death due to any cause. Confirmed ORR was defined as the proportion of patients that had achieved complete response (CR) or partial response (PR) as determined by the BIRC per RECIST 1.1. Tumor response was confirmed ≥ 4 weeks after the initial response was observed. Disease control rate was defined as the proportion of randomized patients that achieve CR, PR, or stable disease for ≥ 6 weeks after randomization. Duration of response was defined as the time from the date that the criteria for CR or PR are first met until the first date that progressive disease is documented. Intracranial ORR was defined as the proportion of randomized patients with intracranial CNS metastases (measurable, non-measurable, or any) at baseline that achieved CR or PR in the CNS, as determined by the BIRC per RECIST version 1.1. Intracranial DOR was defined as the time from the date that the criteria for CR or PR are first met until the first date that progressive disease is documented. Intracranial PFS was defined as the time from the day of randomization until the first day CNS disease progression is documented or death due to any cause (whichever occurs first) in patients with any intracranial CNS metastases at baseline.

For PFS and OS, median values and 95% CIs were estimated for each study group using the Kaplan-Meier (KM) method, and HRs were estimated using the Cox regression models, with the stratification factors as covariates. Confirmed ORR was assessed base on the Mantel-Haenszel test (including the stratification factors) to compare the proportion of patients achieving object response between the two study groups. Exact 2-sided 95% binomial CIs were calculated.[3]

The EORTC QLQ-C30 (v3.0) and EORTC QLQ-LC13 (v3.0) questionnaires were administered to patients in their local language at baseline, day one of every four-week cycle during treatment, at the end of treatment, and 30 days after the last dose. The questionnaires were administered when patients arrived at their scheduled visits prior to the completion of other assessments and procedures. Only patients with a baseline assessment and at least one post-baseline assessment were included in the analyses.[3] The EORTC QLQ-LC13 instrument was added as a QOL assessment in protocol amendment 1.[3] Patients enrolled after the protocol amendment who had a baseline QLQ-LC13 assessment were included in the QLQ-LC13 analysis.[3] The EORTC QLQ-C30 was scored on five functional scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and

nausea/vomiting), and a GHS/QoL scale.[1] The trial also included six single-item symptom scales from the EORTC QLQ-C30: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.[1] The QLQ-LC13 is specific to lung cancer, and assesses lung cancer symptoms (coughing, hemoptysis, dyspnea, and pain) and side effects from treatment (hair loss, neuropathy, sore mouth and dysphagia). All scales from both instruments range from 0 to 100, with higher scores representing a higher response level (i.e., a high score on a function score represents a high level of functioning versus a high score on a symptom scale represents a high level of symptomatology). The original analysis plan defined the minimum important difference (MID) as 8.33 points. Analyses were also conducted using a mean change from baseline of ≥ 10 points as the MID.[2] Change from baseline scores in GHS/QOL was assessed using mixed effects models including randomized treatment group and the stratification factors used in randomization. Improvement in the GHS/QOL score was analyzed using the Mantel-Haenszel test as performed for ORR.[3] Time to worsening in GHS/QOL and the Dyspnea Scale was analyzed using the same methods as for the primary analyses of PFS. [3] Worsening on the Dyspnea Scale for a patient was defined as a 50% decline from the baseline score.[1] All results for patient-reported outcomes were analyzed descriptively.[3]

Post hoc analyses included time to worsening (defined as 10 points worsening from baseline) and change from baseline (using linear mixed models), in all other subscales of EORTC QLQ-C30 and LC13. Duration of improvement in GHS/QOL and all other subscales of EORTC QLQ-C30 and LC13 was also assessed and defined as the date of first improvement (defined as 10 points improvement from baseline) to the date of first worsening (defined as 10 points worsening from baseline) after the improvement.[3]

Disease Assessment: Disease assessment included imaging of the chest and abdomen using CT scans or MRI with contrast, and contrast-enhanced MRI of the brain. Disease assessment occurred at screening, every 8 weeks during treatment, and at the end of treatment. More frequent imaging was recommended if clinically indicated. Confirmation of CR or PR was performed at least 4 weeks after initial response.

Power Calculation and Sample Size: Sample size was calculated assuming a median PFS of 10 months for crizotinib.[1] Approximately 270 participants needed to be randomized for a total of 198 events (progression or death) to achieve 90% power to detect a 6-month improvement in PFS (HR, 0.625) at the final primary outcome analysis.[1] This power projection is based on a two-sided log-rank test and is controlled at the overall two-sided 0.05 level, adjusting for the two planned interim analyses.[1]

Interim and Final Analyses: Two interim analyses were planned for after approximately 50% (N = 99) and 75% (N = 149) of expected PFS events (disease progression or death) occurred. The overall two-sided type I error for the primary outcome (PFS by BIRC) was controlled at 0.05 using an O'Brien-Fleming Lan-DeMets alpha spending function. In the first and second interim analyses, the primary endpoint was tested at a two-sided α level of 0.0031 and 0.0183, respectively.[3] The final analysis for the primary outcome was planned to be performed after 198 events are observed, and BIRC-assessed PFS will be tested at a two-sided α level of 0.044. The final analysis is expected to be completed in June 2021 as a landmark analysis. Once the primary endpoint will be met, the inferential statical evaluation will be complete and all subsequent analyses of the primary endpoint (including pre-specified subsequent analyses of the primary endpoint) will be non-inferential and descriptive.[3]

For the key secondary endpoints, the type I error rate was controlled at 0.05 using a closed testing procedure. Analysis of an outcome is considered significant if the test for that outcome and comparisons of all other higher-priority secondary outcomes are significant at the two-sided 0.05 level. The rank-ordering of key secondary outcomes is as follows:

1. Confirmed ORR by BIRC
2. Confirmed Intracranial ORR by BIRC
3. Intracranial PFS by BIRC
4. OS

The primary assessments of the key secondary outcomes were planned for when the primary endpoint was met except for OS. The primary assessment of OS was planned to be performed after approximately 150 OS events were observed, approximately three years after the last patient was enrolled.[3]

Data Cut-offs: The data cut-off for the first interim analysis was February 19, 2018, representing a median follow-up time of 11.0 months in the brigatinib group and 9.3 months in the crizotinib group.[1] The data cut-off for the second interim analysis was June 28, 2019, representing a median follow-up of 24.9 months in the brigatinib group and 15.2 months in the crizotinib group.[2]

Analysis Set: All efficacy analyses, including secondary outcomes, were performed in the ITT population. The primary analysis of the primary outcome (PFS by BIRC) was stratified by presence of brain metastases at baseline (Yes vs. No) and prior chemotherapy for locally advanced or metastatic disease (Yes vs. No). Health-related quality of life data (EORTC QLQ-C30 and QLQ-LC13) was

analyzed in patients with a baseline assessment and ≥ 1 post-baseline assessments. Safety analyses were performed in the treated population (i.e., participants that received at least one dose of study drug).

Protocol Amendments: Two protocol amendments were implemented during the conduct of the study.[3] In the first amendment (dated September 21, 2016), the EORTC QLQ-LC13 was added as a HRQoL assessment and the required duration of contraceptive use after the end of treatment was changed to be consistent with crizotinib's Summary of Product Characteristics. Further modifications to the protocol were minor wording changes and additional text to clarify eligibility criteria and study procedures. The second amendment (dated May 17, 2018) disallowed hormonal contraception as an effective method of contraception during study participation because brigatinib may result in decreased efficacy of hormonal contraceptives.

b) Populations

A total of 275 patients were randomized in the ALTA-1L trial, with 137 allocated to brigatinib and 138 allocated to crizotinib.[1] The baseline characteristics of patients are summarized in Table 8. Overall, the distributions of baseline characteristics between the treatment groups were well-balanced. The median age of patients was 59 years old, with a range of 27 to 89 years. Most patients were female (55%), of non-Asian race (61%), never smoked (58%), and had an ECOG status of 0 or 1 (96%). Most of the non-Asian patients were white (97%). Most patients had metastatic disease (93%) and adenocarcinoma histological type (96%). Overall, 27% (N = 81) of patients had received previous chemotherapy, including adjuvant chemotherapy (7%), neoadjuvant chemotherapy (3%), chemotherapy for advanced or metastatic disease (22%), and other chemotherapy (1%), at study entry.[3,66] Previous chemotherapies included cisplatin, carboplatin, pemetrexed, vinorelbine, etoposide, paclitaxel, docetaxel, and gemcitabine.[66] The most common reasons for stopping their previous chemotherapy included completion of therapy (N = 36, 13%), resistance (N = 24, 9%), and intolerance (N = 10, 4%).[66] Approximately 27% of patients had prior radiation therapy (24% in the brigatinib group and 29% in the crizotinib group).[1,3] Brain metastases were present in 29% of patients at baseline as assessed by the investigator. Approximately 13% of patients had received radiotherapy to the brain.

Table 8: Baseline patient characteristics of the ALTA-1L Trial

Table 1. Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Brigatinib (N=137)	Crizotinib (N=138)	Total (N=275)
Age — yr			
Median	58	60	59
Range	27–86	29–89	27–89
Female sex — no. (%)	69 (50)	81 (59)	150 (55)
Race — no. (%)†			
Non-Asian	78 (57)	89 (64)	167 (61)
Asian	59 (43)	49 (36)	108 (39)
ECOG performance-status score — no. (%)‡			
0 or 1	131 (96)	132 (96)	263 (96)
2	6 (4)	6 (4)	12 (4)
History of tobacco use — no. (%)			
Never smoked	84 (61)	75 (54)	159 (58)
Former smoker	49 (36)	56 (41)	105 (38)
Current smoker	4 (3)	7 (5)	11 (4)
Stage of disease at trial entry — no. (%)			
IIIB	8 (6)	12 (9)	20 (7)
IV	129 (94)	126 (91)	255 (93)
Histologic type — no. (%)			
Adenocarcinoma	126 (92)	137 (99)	263 (96)
Adenosquamous carcinoma	3 (2)	1 (1)	4 (1)
Squamous-cell carcinoma	4 (3)	0	4 (1)
Large-cell carcinoma	2 (1)	0	2 (1)
Other	2 (1)	0	2 (1)
ALK status assessed locally with the use of FDA-approved test — no. %§	123 (90)	112 (81)	235 (85)
Brain metastases — no. (%)¶	40 (29)	41 (30)	81 (29)
Previous radiotherapy to brain — no. (%)	18 (13)	19 (14)	37 (13)
Previous chemotherapy in patients with locally advanced or metastatic disease — no. (%)‖	36 (26)	37 (27)	73 (27)

ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration

Source: From the New England Journal of Medicine, Camidge et al, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, 379, 2027-2039. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

* Percentages may not sum to 100 because of rounding.
† Race was reported by the investigator.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating increasing impairment in activities of daily living.
§ ALK-positive status was confirmed locally by fluorescence in situ hybridization (Vysis) or immunohistochemical assay (Ventana).
¶ The presence of brain metastases was assessed by the investigator.
‖ Previous chemotherapy was defined as completion of at least one full cycle of chemotherapy in patients with locally advanced or metastatic disease. Among 36 patients who received previous chemotherapy in the brigatinib group, 2 (6%) had a complete response, 9 (25%) had a partial response, 10 (28%) had stable disease, and 8 (22%) had progressive disease; the best response to previous chemotherapy was "other or unknown" in 7 patients (19%). Among 37 patients who received previous chemotherapy in the crizotinib group, 2 (5%) had a complete response, 8 (22%) had a partial response, 13 (35%) had stable disease, and 7 (19%) had progressive disease; the best response to previous chemotherapy was "other or unknown" in 7 patients (19%).

c) Interventions

Treatment Dosing Schedule

Patients were treated with either brigatinib orally at a dose of 90 mg once daily for 7 days followed by 180 mg once daily continuously, or crizotinib orally at a dose of 250 mg twice daily.[1] Patients continued study treatments until they experienced BIRC-assessed disease progression, unacceptable toxicity, or were discontinued for other reasons (discontinuation criteria included: entry into another clinical study, start of a new anticancer therapy, significant deviation from the protocol or eligibility criteria, non-compliance with study procedures, pregnancy). After experiencing progressive disease per RECIST version 1.1, participants in the brigatinib group could continue the study treatment if they continue to experience clinical benefit in the opinion of the investigator, and patients in the crizotinib group could crossover from crizotinib to brigatinib (following a ≥ 10 day washout period from crizotinib) at the investigator's discretion.[1,2]

Dose Modifications, Interruptions, or Reductions

Dose interruptions or modifications were implemented for patients who experienced treatment-related AEs, including during the 7-day lead-in period for patients in the brigatinib group.[1] Study drug administration could be delayed up to 28 days to allow AEs to resolve. Dose modifications, interruptions, and reductions were allowed in both study groups per the ALTA-1L trial protocol.

During the 7-day lead-in period (prior to dose escalation to 180 mg/day) in the brigatinib group, if a grade 3 or 4 AE other than pneumonitis occurred, the recommended action was to withhold brigatinib until the event was a lower grade or returned to baseline, then resume at 90 mg per day. If grade 1 or 2 pneumonitis occurred, it was recommended to withhold brigatinib until return to grade 0 (baseline), then resume treatment with brigatinib at 90 mg/day or 60 mg/day, respectively. If pneumonitis recurred, brigatinib treatment was permanently discontinued. If grade 3 or 4 pneumonitis occurred, brigatinib treatment was permanently discontinued.

After dose escalation to 180 mg/day in the brigatinib group, if a grade 3 AE other than pneumonitis occurred, it was recommended to hold brigatinib until the until the event is ≤ grade 2 or returned to baseline, then resume at 180 mg or 120 mg at the investigator's discretion. If a grade 4 AE other than pneumonitis occurred after dose escalation, it was recommended to hold until the until the event was ≤ grade 1 or 2 or returned to baseline, then resume at 120 mg. If the AE recurred, it was recommended to hold until the event is a lower grade and resume at a lower dose. If grade 1 or 2 pneumonitis occurred after dose escalation to 180 mg/day, it was recommended to withhold the dose until return to grade 0 (baseline), then resume treatment with brigatinib at 180 mg/day or 120 mg/day, respectively. If pneumonitis recurred, brigatinib treatment was permanently discontinued. If grade 3 or 4 pneumonitis occurred, brigatinib treatment was permanently discontinued.

In the crizotinib group, if a grade 3 or 4 hematologic toxicity occurred, it was recommended to withhold crizotinib until recovery to ≤ grade 2 then resume at the same dose schedule or 200 mg twice per day, respectively. It was also recommended to withhold crizotinib if grade 3 QTc prolongation or grade 2-3 bradycardia occurred. If any interstitial lung disease/pneumonitis or grade 4 QTc prolongation occurred, crizotinib was permanently discontinued.

During the ALTA-1L trial, 65% of patients in the brigatinib group and 51% of patients in the crizotinib group had at least 1 dose interruption of ≥ 3 days.[3] Overall, 38% of patients in the brigatinib group and 25% of patients in the crizotinib group had dose reductions due to AEs. Dose interruptions due to AEs were reported in 66% of patients in the brigatinib group and 47% of patients in the crizotinib group.

Exposure to Study Treatment

Median time on randomized study treatment was 24.3 months in the brigatinib group and 8.4 months in the crizotinib group.[3] Median dose intesity was 163.83 mg/day in the brigatinib group and 495.64 mg/day in the crizotinib group. Median relative dose intensity was 96.89% in the brigatinib group and 99.12% in the crizotinib group.

Concomitant Therapies

Patients could receive palliative therapy and supportive care to manage symptoms and underlying medical conditions.[1] If the patient required local radiotherapy for CNS lesions or emergency surgery, they could have an interruption of study therapy to receive the treatment. In the treated population (N = 136 in the brigatinib group, N = 137 in the crizotinib group), approximately 100% (N = 136 in the brigatinib group, N = 136 in the crizotinib group) of patients received any concomitant medication.[66] The concomitant medications were expected for the study population and there were no significant differences between treatment groups.[66] The most commonly received concomitant medications in the brigatinib and crizotinib groups were paracetamol (55% and 36%, respectively), dexamethasone (18% and 15%, respectively), omeprazole (18% and 15%, respectively), furosemide (13% and 18%, respectively), and metoclopramide hydrochloride (12% and 18%, respectively).[66]

Other systemic anticancer therapies, medications associated with causing Torsades de Pointes, and surgery requiring inpatient care were prohibited. In addition, chemotherapy and radiation (excluding stereotactic radiosurgery or stereotactic body radiation therapy prohibited within 14 days of the first study drug dose. Antineoplastic monoclonal antibodies and major surgery within 30 days of the first study drug dose were also prohibited.

Subsequent Treatments

Follow-up assessments to capture subsequent anticancer therapies received by participants were performed every 12 weeks ± 14 days after the last dose of the assigned study drug.[1] Details regarding the types of subsequent treatments received by patients in both groups of the ALTA-1L trial are summarized in Table 9. In the brigatinib group, 25% of patients received at least one subsequent systemic anticancer therapy compared to 70% of patients in the crizotinib group. Overall, 22% of patients in the brigatinib group and 67% in the crizotinib group received a TKI as a subsequent treatment. A total of 61 (44%) crizotinib patients crossed over to brigatinib in ALTA-1L following documented PD or radiotherapy to the brain as per trial protocol (also known as ‘official switchers’). An additional 12 crizotinib patients, not included in the ‘official switchers’ group, were identified as having switched based on their concomitant/subsequent medicine records (i.e., a total of 73 patients switched from crizotinib to brigatinib)

Table 9: Subsequent treatments received by patients enrolled in the ALTA-1L trial

Subsequent Anti-Cancer Treatment	Brigatinib ALTA-1L (N = 137)	Crizotinib ALTA-1L (N = 138)
Surgery, N (%)	0	2 (1.4)
Radiotherapy, N (%)	1 (0.7)	11 (8.0)
Systemic Therapy, N (%)	34 (24.8)	96 (69.6)
ALK TKI, N (%)	30 (21.9)	93 (67.4)
Alectinib	10 (7.3)	24 (17.4)
Alectinib hydrochloride	0	1 (0.7)
Brigatinib	1 (0.7)	73 (52.9)
Ceritinib	4 (2.9)	4 (2.9)
Crizotinib	11 (8.0)	6 (4.3)
Lorlatinib	13 (9.5)	11 (8.0)
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	NA	NA
Chemotherapy N (%)	13 (9.5)	13 (9.4)
Immunotherapy N (%)	3 (2.2)	4 (2.9)
VEGF-R N (%)	3 (2.2)	4 (2.9)
Other, N (%)	2 (1.5)	1 (0.7)

ALK = anaplastic lymphoma kinase; TKI = tyrosine kinase inhibitor; NA = not applicable; VEGF-R = vascular endothelial growth factor receptor

Source: Response to pCODR checkpoint meeting questions.[66]

d) Patient Disposition

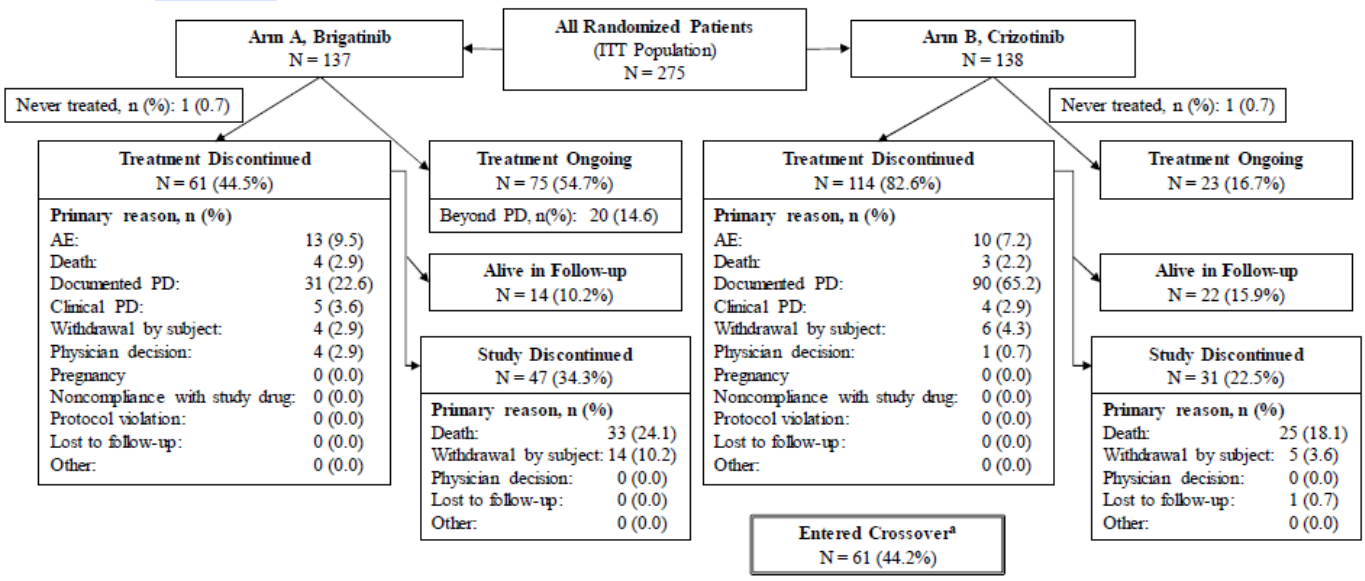
Patient disposition in the ITT population of the ALTA-1L trial as of the second interim analysis (June 28, 2019 data cut-off date) is presented in Figure 3. A total of 275 patients were randomized to receive either brigatinib (N = 137) or crizotinib (N = 138).[2] One patient in the brigatinib group and one in the crizotinib group did not receive their assigned treatments while 55% of patients (N = 75) were still receiving brigatinib and 17% of patients (N = 23) were still receiving crizotinib. In the brigatinib group, 15% of patients remained on treatment after experiencing progressive disease.[3] In the brigatinib group, 34% (N = 47) of patients discontinued the study compared to 23% (N = 31) of patients in the crizotinib group. The most common primary reason for study discontinuation was death (24% in the brigatnib group and 18% in the crizotinib group).

In the brigatinib group, 45% of patients (N = 61) had discontinued their assigned treatment while 83% of patients (N = 114) in the crizotinib group discontinued treatment. The most common reason for treatment discontinuation in both the brigatinib and crizotinib groups was progressive disease (59% vs. 82%). Three percent (N = 4) of patients in the brigatinib group and 4% (N = 6) of patients in the crizotinib group discontinued their treatment because they withdrew consent. Overall, 7% (N = 19) of participants withdrew consent over the course of the study. From the crizotinib group, 44% of patients (N = 61) crossed over to brigatinib and 57% (N = 35) of those patients were continuing to receive brigatinib. Additional patients (N = 12) in the crizotinib group received brigatinib as a subsequent therapy after coming off study (‘unofficial switchers’). No patients in the brigatinib group and one patient in the crizotinib group had been lost to follow-up.

Protocol Deviations

As of the June 28, 2019 data cut-off for the second interim analysis, 157 (57%) of patients had ≥ 1 major protocol deviation, which included 82 (60%) patients in the brigatinib group and 75 (54%) patients in the crizotinib group. Overall, the most frequent types of protocol deviations were procedures not done per protocol (38%), study objective or safety (17%), visit out of window (8%), and study medication (8%). Each of the most common types of protocol deviations occurred more frequently in the brigatinib group. Most procedures not done per protocol and study objective or safety deviations were related to a laboratory parameter (e.g., creatine kinase, direct bilirubin, CO_2, or insulin) not tested at a visit. Most study medication deviations were related to patient compliance (e.g., missing dose of study drug) or site staff documentation errors.

Figure 3: Patient disposition in the ALTA-1L Trial as of the June 28, 2019 cut-off date



Source: IA2 Table 15.1.3 and 15.1.3.1 (data cutoff: 28 June 2019).
AE: adverse event; ITT: intent to treat; PD: progressive disease.
Percentages are based on the number of patients randomized.
[a] Thirty-five (57.4%) of subjects who entered crossover were continuing to receive brigatinib as study drug at the data cutoff.

Source: Clinical study report[3]

e) Limitations/Sources of Bias

A stratified randomization procedure was used based on clinical factors to minimize potential imbalances between the study groups that might lead to biased results. The populations used for the analyses were appropriate, with the key efficacy analysis conducted according to the ITT principle. Statistical adjustment was made for the repeated analysis of the primary and key secondary endpoints. Eligibility criteria were well defined and appropriate. In addition, baseline characteristics were representative of the patient population seen in Canadian practice. However, the following limitations were noted:

- Based on the guidance from the clinical experts consulted by CADTH, alectinib is the ALK inhibitor of choice in the first line setting for patients newly diagnosed with ALK-positive NSCLC in Canadian practice. The shift from crizotinib to alectinib in the first-line setting occurred in response to the results of the Global ALEX[4] and J ALEX trials[5], where alectinib demonstrated improved PFS compared to crizotinib. Although crizotinib was the most appropriate comparator when the ALTA-1L trial was designed, alectinib is the most commonly used first-line treatment in current Canadian practice.
- The open-label design of the trial makes it prone to different biases (patient selection bias, performance bias, detection bias), which can affect internal validity. The investigators, trial, personnel, and patients were all aware of study drug assignment, which

could potentially bias outcome assessment in favour of brigatinib if assessors (investigators and patients) believe brigatinib is likely to provide benefit. An attempt was made to mitigate bias by using BIRCs to assess outcomes using standardized criteria (RECIST version 1.1). However, for subjective outcomes like HRQoL and AEs, there is a greater risk of bias because patients and investigators would be aware of the specific treatment being administered. The magnitude and direction of this bias is uncertain, although it is plausible that it would be in favour of the new treatment.

- The two data cut-off dates of February 19, 2018 and July 28, 2019 represent interim analyses of the ALTA-1L trial. At the first interim analysis, median follow-up times for patients in the brigatinib and crizotinib groups were 11.0 months and 9.3 months, respectively. At the second interim analysis, median follow-up times for patients in the brigatinib and crizotinib groups were 24.9 months and 15.2 months, respectively. The OS data is immature because the primary analysis of OS was planned to occur approximately three years after the last patient was enrolled and 150 OS events were observed. Follow-up for long-term survival is ongoing and analysis is planned to be completed in June 2021 as a non-inferential landmark analysis. Due to OS data immaturity and median OS not been reached in either study group, the actual degree of long-term benefit of brigatinib treatment is unknown.
- Only the primary and key secondary endpoints were adjusted for multiplicities. For other secondary outcomes (including DOR and HRQoL) and exploratory outcomes, P values were for descriptive purposes only and were not controlled for type 1 error. Subgroup and sensitivity analyses were prespecified, though not adjusted for multiplicity as well. These analyses should be considered exploratory and interpreted with caution.
- There are limitations associated with the HRQoL data. First, the EORTC QLQ-LC13 was added to the ALTA-1L trial in protocol amendment 1. Only patients enrolled after the protocol amendment provided a baseline EORTC QLQ-LC13 assessment and could be included in the analysis. As of the second interim analysis, 63 (46%) patients in the brigatinib group and 78 (57%) patients in the crizotinib group completed the EORTC QLQ-LC13 scale at baseline and ≥ 1 post-baseline assessments. Due to the proportion of patients included in the QLQ-LC13 analysis, it is possible that this instrument did not fully capture the HRQoL experience of all patients in the trial. Second, the number of patients who provided assessments gradually decreased over treatment cycles and therefore results at later cycles may not be interpretable due to the small sample size. Lastly, only the analyses of the change from baseline scores in GHS/ QoL assessed with the EORTC QLQ-C30, and time-to-deterioration in dyspnea assessed with the EORTC QLQ-LC13 were pre-planned. All other analyses (e.g., duration of improvement in EORTC QLQ-C30 GHS/QoL responders) were post-hoc.
- Overall survival data are confounded by crossover of patients in the crizotinib group to brigatinib and subsequent use of other anticancer therapies (including TKIs) by patients in both groups after discontinuation of the study treatment. Overall, 25% of patients in the brigatinib group received a subsequent systemic anticancer therapy compared to 70% of patients in crizotinib. In the brigatinib group, 22% of patients received an ALK TKI as a subsequent treatment compared to 67% of patients in crizotinib group. From the brigatinib group, 11 (8%) patients received crizotinib as a subsequent treatment. From the crizotinib group, 73 (53%) of patients received brigatinib, including the 61 (44%) patients that formally crossed over to brigatinib per the ALTA-1L trial. Subsequent treatments and crossover may have prolonged survival beyond what would have occurred had the patients only received their randomized study treatment. The ALTA-1L protocol pre-planned exploratory sensitivity analyses to adjust for crossover effects. The marginal structural model (MSM), the inverse probability of censoring weights (IPCW) and the rank preserving structural failure time model (RPSFTM; with and without re-censoring) methods were used to attempt to adjust for bias introduced from patients switching from crizotinib to brigatinib. The following key limitations associated with the analyses were noted. OS data are immature, with a total of only 70 deaths reported as of the second interim analysis, including 33 (24%) patients in the brigatinib group and 37 (27%) patients in the crizotinib group. An abstract reporting the results of these analyses identified limitations due to difficulties validating the requirements underpinning treatment switching methodologies and not accounting for other subsequent ALK inhibitor use.[6] Given the immature OS data, and likely biases with the treatment switching adjustments analyses methods, the Methods Team cannot firmly conclude that the analyses adequately adjusts for the confounding effects of crossover.
- The ALTA-1L trial is an industry-funded trial. The staff and representatives of the sponsor were involved in all aspects of conducting the study (e.g., design, data collection, analyses, interpretation, and preparation of the manuscripts). Therefore, a potential for conflict of interest exists, which would risk the objectivity in the conduct of the study as well as the reporting and interpretation of findings.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy outcomes in the ALTA-1L trial were assessed at two prespecified interim analyses with data cut-offs of February 19, 2018 and June 28, 2019. The results of both analyses are summarized in Table 10 for systemic efficacy outcomes and Table 11 for CNS efficacy outcomes.

Table 10: Systemic Efficacy Outcomes in the ITT Population of ALTA-1L Trial

Interim Analysis	First Interim Analysis		Second Interim Analysis	
Data Cut-Off Date	February 19, 2018		June 28, 2019	
Treatment Arms	Brigatinib (n=137)	Crizotinib (n=138)	Brigatinib (n=137)	Crizotinib (n=138)
Median follow-up time in months (range)	11.0 (0 – 20.0)	9.3 (0 – 20.9)	24.9 (0 – 34.1)	15.2 (0.1 – 36.0)
Median duration of treatment in months (range)	9.2 (0.1 – 18.4)	7.4 (0.1 – 19.2)	24.3 (0.1–34.6)	8.4 (0.1 – 36.0)
Primary outcome: PFS by BIRC				
Events, N (%)	36 (26)	63 (46)	63 (46)	87 (63)
Median in months (95% CI)	NR (NR – NR)	9.8 (9.0 – 12.9)	24.0 (18.5 – NR)	11.0 (9.2 – 12.9)
HR (95% CI); *P* value	0.49 (0.33 – 0.74); *P* < 0.001		0.49 (0.35 – 0.68); *P* < 0.0001*	
Key secondary outcomes				
OS				
Events, N (%)	17 (12)	17 (12)	33 (24)	37 (27)
Median in months (95% CI)	NR (NR – NR)	NR (NR – NR)	NR (NR – NR)	NR (NR – NR)
HR (95% CI); *P* value	0.98 (0.50 – 1.93); *P* = 0.9611*		0.92 (0.57 – 1.47); *P* = 0.771*	
KM estimated rate of 12-month OS, % (95% CI)	85 (76 – 91)	86 (77 – 91)	85 (78 – 90)	87 (80 – 91)
Confirmed ORR by BIRC				
N	97	83	101	85
% (95% CI)	71 (62 – 78)	60 (51 – 68)	74 (66 – 81)	62 (53 – 70)
CR, N (%)	5 (4)	7 (5)	20 (15)	12 (9)
PR, N (%)	92 (67)	76 (55)	81 (59)	73 (53)
OR (95% CI); *P* value	1.59 (0.96 – 2.62); *P* = 0.0678		1.73 (1.04 – 2.88); *P* = 0.0342*	
DCR				
Median % (95% CI)	85 (78 – 90)	86 (79 – 92)	85 (78 – 90)	86 (79 – 92)
OR (95% CI); *P* value	0.93 (0.47 – 1.82); *P* = 0.8220*		0.93 (0.47 – 1.82); *P* = 0.8220*	
DOR				
Median in months (95% CI)	NR (NR – NR)	11.1 (9.2 – NR)	NR (19.4 – NR)	13.8 (9.3 – 20.8)

Interim Analysis	First Interim Analysis		Second Interim Analysis	
Data Cut-Off Date	February 19, 2018		June 28, 2019	
Treatment Arms	Brigatinib (n=137)	Crizotinib (n=138)	Brigatinib (n=137)	Crizotinib (n=138)
KM estimated rate of 12-month DOR, % (95% CI)	75 (63 – 83)	41 (26 – 54)	78 (68 – 85)	54 (42 – 65)

BIRC = blinded independent review committee; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; KM = Kaplan-Meier; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response

* Nominal *P* value (i.e., results are non-inferential)

Data sources: Camidge at al. 2018,[1] Camidge et al. 2020,[2] EPAR 2020,[7] Response to pCODR checkpoint meeting questions[66]

Table 11: CNS Efficacy Outcomes in the ALTA-1L Trial

Interim Analysis	First Interim Analysis		Second Interim Analysis	
Data Cut-Off Date	February 19, 2018		June 28, 2019	
Treatment Arms	Brigatinib	Crizotinib	Brigatinib	Crizotinib
ITT Population				
N	137	138	137	138
Intracranial PFS by BIRC, median (95% CI)	NR (NR – NR)	NR (11.1 – NR)	32.3 (29.5 – NR)	24.0 (12.9 – NR)
HR (95% CI); *P* value	0.42 (0.24 – 0.70); *P* = 0.0011*		0.45 (0.29 – 0.69); *P* = 0.0001*	
Patients with any intracranial CNS metastases at baseline				
N (%)	43 (31)	47 (34)	47 (34)	49 (36)
Intracranial PFS by BIRC, median (95% CI)	NR (11.0 – NR)	5.6 (4.1 – 9.2)	24.0 (12.9 – NR)	5.6 (3.7 – 7.5)
HR (95% CI); *P* value	0.27 (0.13 – 0.54); *P* = 0.0002*		0.31 (0.17 – 0.56); *P* < 0.0001*	
Confirmed intracranial CNS ORR, % (95% CI)	67 (51 – 81)	17 (8 – 31)	66 (51 – 79)	16 (7 – 30)
Responders, N	29	8	31	8
CR, N (%)	16 (37)	2 (4)	21 (45)	2 (4)
PR, N (%)	13 (30)	6 (13)	10 (21)	6 (12)
OR (95% CI); *P* value	13.00 (4.38 – 38.61); *P* < 0.0001*		11.75 (4.19 – 32.91); *P* < 0.0001*	
Intracranial CNS DOR in months, median (95% CI)	NR (NR – NR)	9.23 (3.88 – 9.23)	24.0 (16.9 – NR)	9.2 (3.9 – NR)
Patients without intracranial CNS metastases at baseline				
N (%)	94 (67)	91 (66)	90 (66)	89 (64)
Intracranial PFS by BIRC, median (95% CI)	NR (NR – NR)	NR (NR – NR)	32.3 (NR – NR)	NR (24.6 – NR)
HR (95% CI); *P* value	0.96 (0.42 – 2.22); *P* = 0.9234*		0.78 (0.41 – 1.48); *P* = 0.3470*	

BIRC = blinded independent review committee; CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; ITT = intention-to-treat; HR = hazard ratio; NE = not evaluable; NR = not reached; ORR = objective response rate; PFS = progression-free survival; PR = partial response

* Nominal *P* value (i.e., results are non-inferential)

Data sources: Camidge at al. 2018,[1] Camidge et al. 2020,[2] EPAR 2020,[7] Response to pCODR checkpoint meeting questions[66], Popat et al. 2020[47]

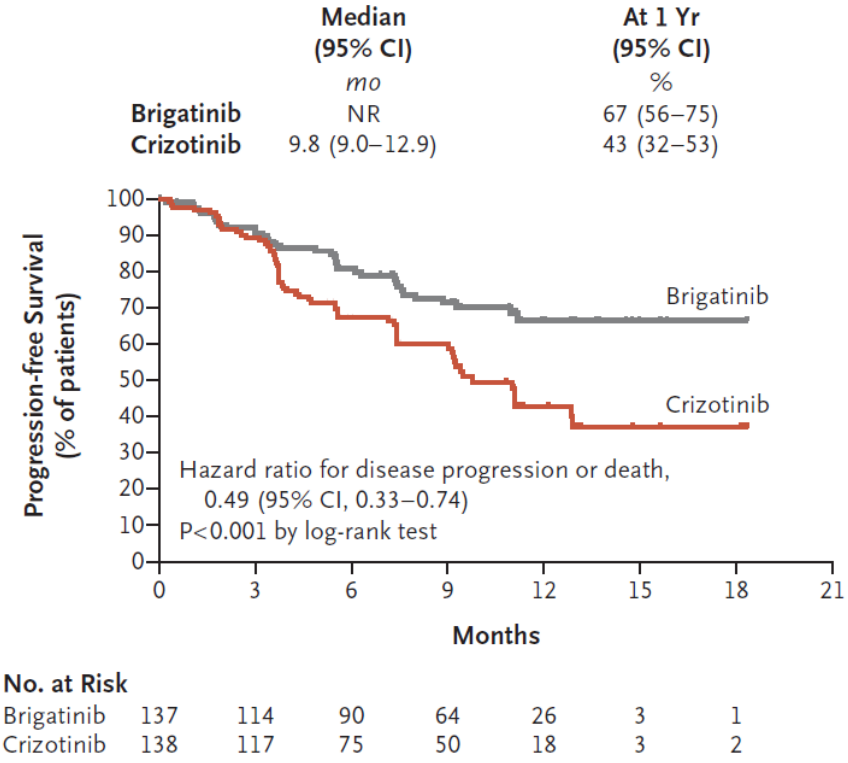
Progression-Free Survival

Progression free survival as assessed by the BIRC was the primary outcome in the ALTA-1L trial.[1]

As of the February 19, 2018 data cut-off for the first interim analysis, 26% of patients in the brigatinib group had a PFS event compared to 46% of patients in the crizotinib group.[1] In the ITT population, the median BIRC-assessed PFS was not reached (NR) in the brigatinib group versus 9.8 months (95% CI, 9.0 – 12.9 months) in the crizotinib group. The Kaplan-Meier curves are presented in Figure 4. Brigatinib was associated with a statistically significant improvement in BIRC-assessed PFS compared to crizotinib (hazard ratio [HR], 0.49; 95% CI, 0.33 – 0.74; $P < 0.001$). By BIRC assessment, the estimated 12-month PFS rate was 67% (95% CI, 56 – 75%) in the brigatinib group versus 43% (95% CI, 32 – 53%) in the crizotinib group. Consistent with BIRC-assessed PFS, PFS by investigator assessment was also increased in patients in the brigatinib group. The estimated 12-month PFS rate was 69% (95% CI, 59 – 76%) in the brigatinib group compared to 40% (95% CI, 30 – 50%) in the crizotinib group (HR, 0.45; 95% CI, 0.30 – 0.68).

In the exploratory subgroup of patients with intracranial CNS metastases at baseline, the median BIRC-assessed PFS was NR (95% CI, NR – NR) in the brigatinib group (N = 40) versus 5.6 months (95% CI, 3.8 – 11.1 months) in the crizotinib group (N = 41) as of the first interim analysis (HR, 0.204; 95% CI, 0.09 – 0.46; $P = 0.0001$).[7] In the subgroup of patients without intracranial CNS metastases at baseline, the median BIRC-assessed PFS was NR (95% CI, NR – NR) in the brigatinib group (N = 97) compared to 11.1 months (95% CI, 9.2 months – NR) in the crizotinib group (N = 97) as of the first interim analysis (HR, 0.723; 95% CI, 0.44 – 1.18; $P = 0.191$).

Figure 4: Kaplan-Meier estimates of BIRC-Assessed PFS in the ITT Population as of the February 19, 2018 cut-off date

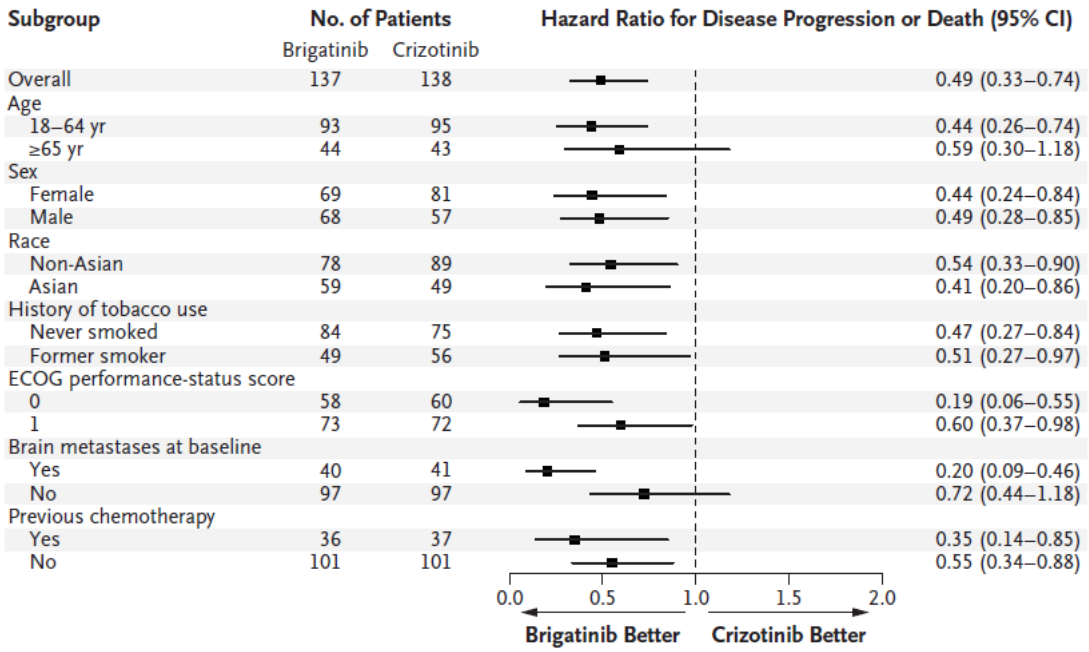


CI = confidence interval; NR = not reached

Source: From the New England Journal of Medicine, Camidge et al, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, 379, 2027-2039. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

Camidge et al. (2018)[1] performed additional exploratory subgroup analyses by baseline potential prognostic factors testing the effect of brigatinib versus crizotinib on PFS (Figure 5).[1] The estimates from the subgroups were consistent with the overall estimates of PFS favouring brigatinib. However, the subgroup analysis did not adjust for stratification factors or multiplicity and thus should be interpreted with caution.

Figure 5: HRs for BIRC-assessed PFS using data from the ALTA-1L trial as of the February 19, 2018 cut-off date



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group

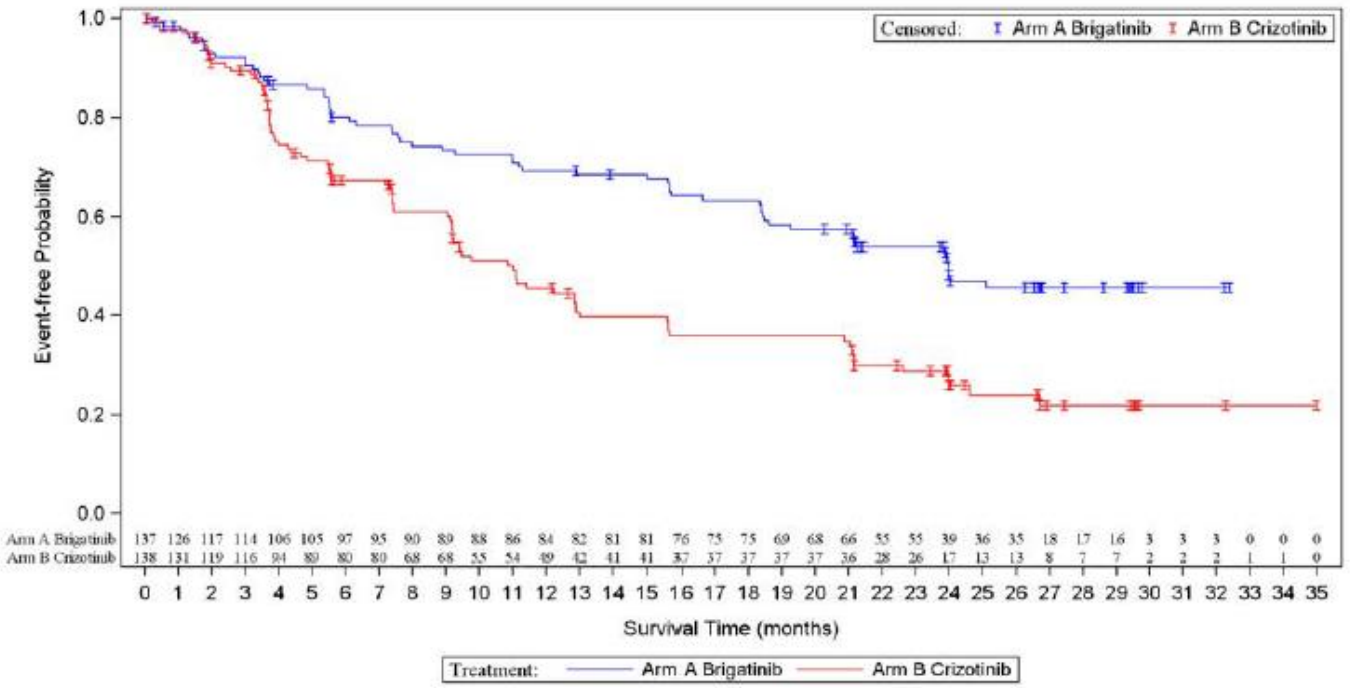
Note: The HR was not calculated for current smokers and patients that had an ECOG performance status score of 2 due to insufficient patient numbers as per the SAP.[3]

Source: From the New England Journal of Medicine, Camidge et al, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, 379, 2027-2039. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

As of the June 28, 2019 data cut-off for the second interim analysis, 46% of patients in the brigatinib group had a PFS event relative to 63% of patients in the crizotinib group.[2] The PFS results at the second interim analysis were consistent with those at the first interim analysis. Since the primary endpoint was met at the first interim analysis subsequent analyses of the primary endpoint are considered non-inferential. The median BIRC-assessed PFS was 24.0 months [95% CI, 18.5 – not reached (NR)] in the brigatinib group versus 11.0 months (95% CI, 9.2 – 12.9 months) with crizotinib. Consistent with the first interim analysis, brigatinib was associated with an improvement in PFS as compared to crizotinib (HR, 0.49; 95% CI, 0.35 – 0.68; $P < 0.0001$). The estimated 24-month BIRC-assessed PFS rate was 48% (95% CI, 39 – 57%) in the brigatinib group versus 26% (95% CI, 18 – 35) in the crizotinib group. The Kaplan-Meier curves are presented in Figure 6. The investigator-assessed PFS 24-month rate was 56% (95% CI, 46 – 64) in the brigatinib group and 24% (95% CI, 16 – 32) in the crizotinib group. In the exploratory subgroup of patients in the crizotinib group that crossed over to brigatinib (N = 61), the median PFS by BIRC, defined as the time from first brigatinib dose until disease progression or death, was 15.6 months.[66]

At the second interim analysis, investigator-assessed PFS was consistent with the BIRC-assed PFS. Median investigator-assessed PFS was 29.4 months (95% CI, 21.2 months – NR) in the brigatinib group compared to 9.2 months (95% CI, 7.4 – 12.9 months) in the crizotinib group (HR, 0.43; 95% CI, 0.31 – 0.61; $P < 0.0001$).[2]

Figure 6: Kaplan-Meier estimates of BIRC-assessed PFS in the ITT population as of the June 28, 2019 cut-off date



Source: IA2 Figure 15.2.1.1.1.1 (data cutoff: 28 June 2019).
BIRC: blinded independent review committee; ITT: intent to treat; PFS: progression-free survival.

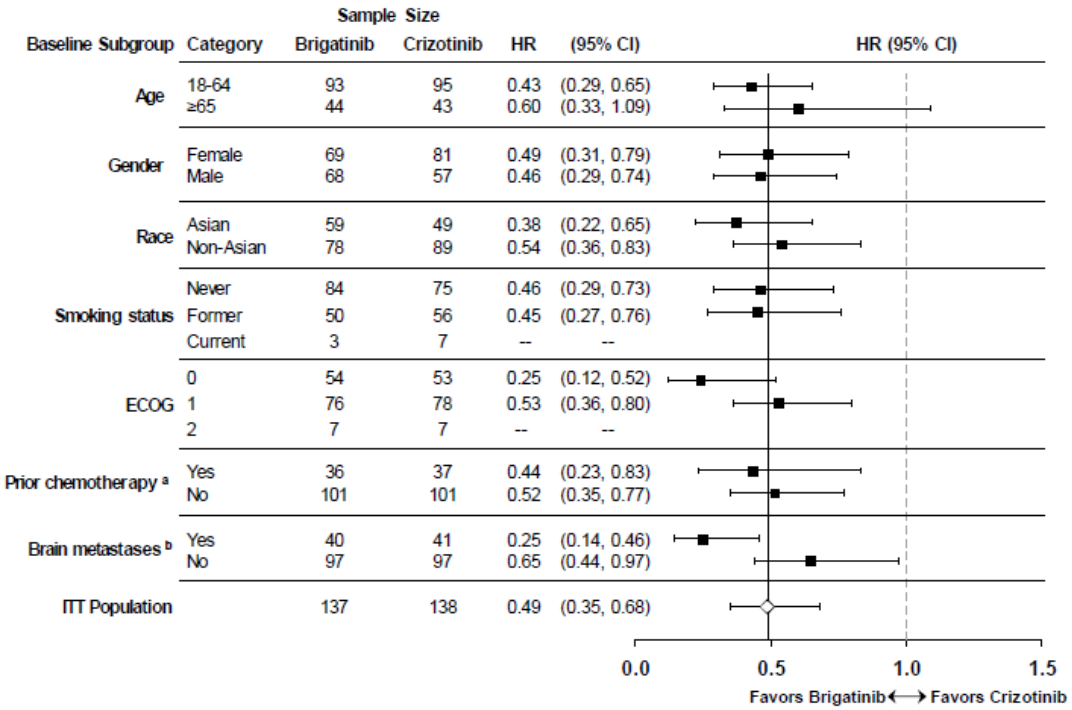
ITT = intention-to-treat; PFS = progression-free survival

Source: Clinical Study Report[3]

At the second interim analysis, PFS was analyzed in the prespecified exploratory subgroups of patients with and without intracranial CNS metastases at baseline. Consistent with the primary analysis in the ITT population, the exploratory subgroup results suggest that brigatinib was associated with improvements in PFS compared to crizotinib in both subgroups. In patients with intracranial CNS metastases at baseline per investigator assessment, median BIRC-assessed PFS was 24.0 months (95% CI, 18.4 months – NR) in the brigatinib group and 5.6 months (95% CI, 3.8 – 9.4 months) in the crizotinib group (HR, 0.25; 95% CI, 0.14 – 0.46; $P < 0.0001$) at the second interim analysis.[2] In patients without intracranial CNS metastases at baseline per investigator assessment, median BIRC-assessed PFS was 24.0 months (95% CI, 15.7 – NR) in the brigatinib group compared to 13.0 months (95% CI, 9.5 – 21.1 months) in the crizotinib group (HR, 0.65; 95% CI, 0.44 – 0.97; $P = 0.030$).[2] The Kaplan-Meier curves for the subgroups of patients with and without intracranial CNS metastases at baseline are presented in Figure 3A and Figure 3B in Camidge et al (2020)[2], respectively.

Camidge et al. (2020)[2] also performed additional exploratory subgroup analyses by baseline potential prognostic factors at the second interim analysis as shown in Figure 7. Similar to the first interim analysis, the estimates from the subgroups were consistent with the overall estimates of PFS favouring brigatinib. The subgroup analysis did not adjust for stratification factors or multiplicity and thus should be considered exploratory and interpreted with caution.

Figure 7 Subgroup analyses - HRs for BIRC-assessed PFS using data from the ALTA-1L trial as of the June 28, 2019 cut-off date



Source: IA2 Figure 15.2.1.1.5.1 and 15.2.1.1.5.2 (data cutoff: 28 June 2019).
BIRC: blinded independent review committee; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT, intent to treat; PFS: progression-free survival.
-- indicates insufficient data to complete the analysis due to small sample size.
[a] Chemotherapy for locally advanced or metastatic disease.
[b] Presence of baseline metastases as determined by the investigator.

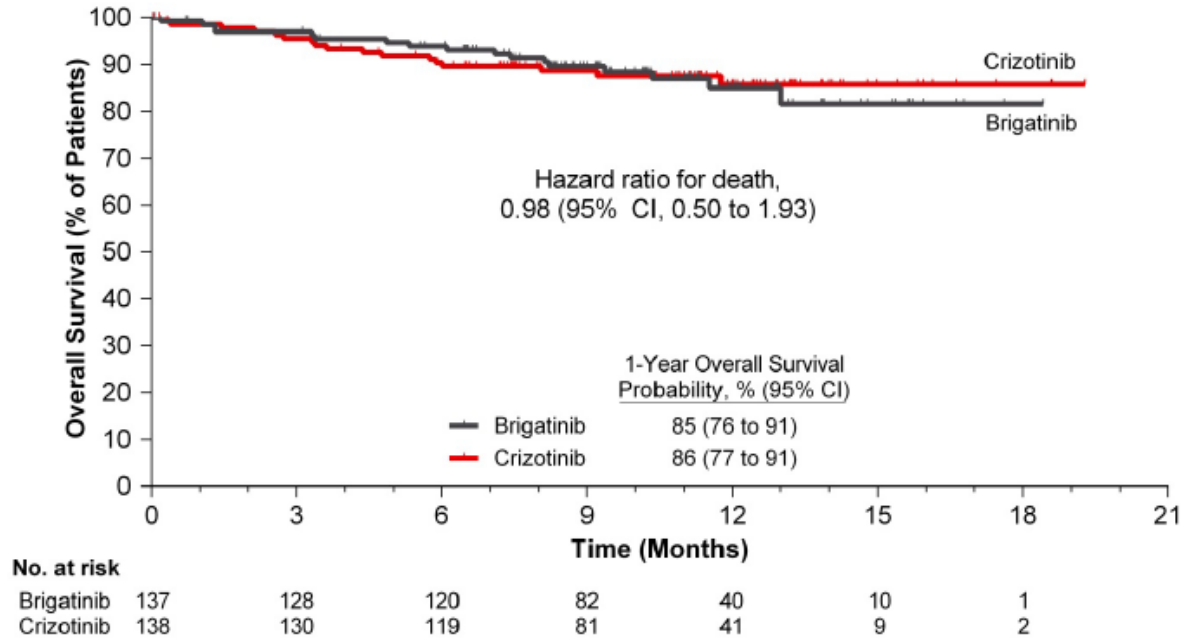
Source: Clinical Study Report[3]

Overall Survival

OS was a key secondary outcome in the ALTA-1L trial.[1]

As of the February 19, 2018 data cut-off for the first interim analysis, 12% (N = 17) of patients in the brigatinib group and 12% (N = 17) of patients in the crizotinib group had died.[1] The median OS was not reached in either treatment group. The Kaplan-Meier curves are presented in Figure 8.The one-year OS probability was 85% (95% CI, 76 – 91%) in the brigatinib group versus 86% (95% CI, 77 – 91%) in the crizotinib group (HR, 0.98; 95% CI, 0.50 – 1.93, nominal *P* = 0.9611).[1,7]

Figure 8: Kaplan-Meier estimates of OS in the ITT population as of the February 19, 2018 cut-off date

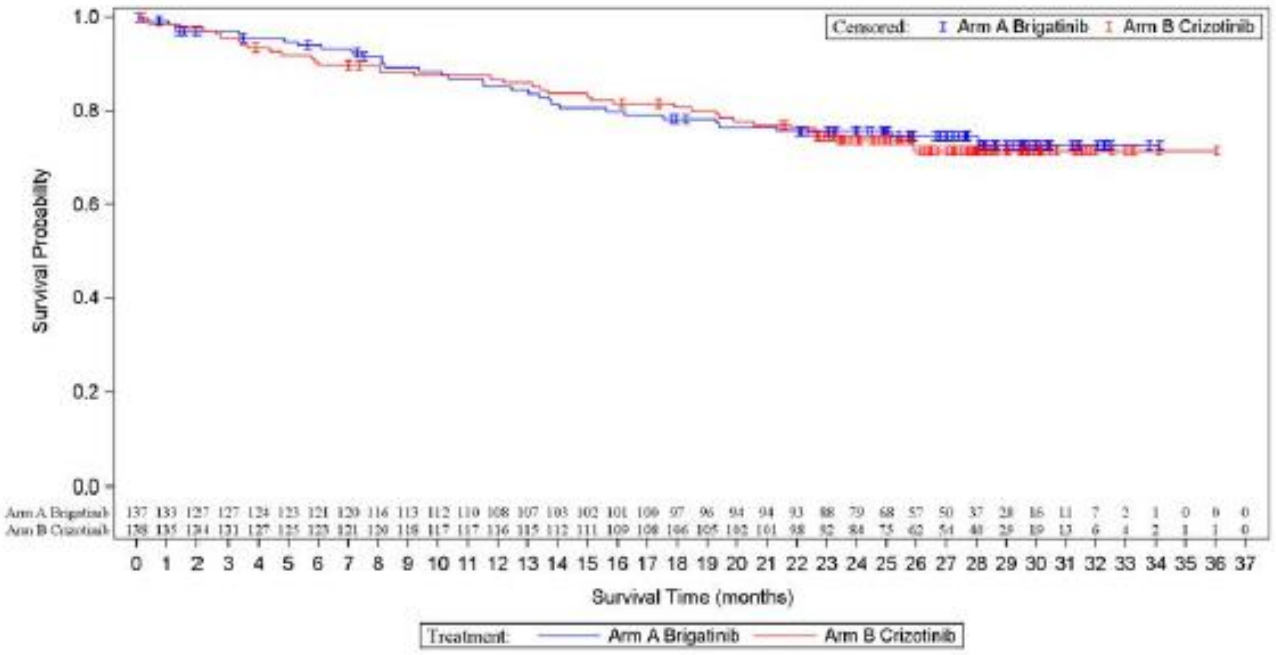


CI = confidence interval

Source: From the New England Journal of Medicine, Camidge et al, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, 379, 2027-2039. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

As of the June 28, 2019 data cut-off for the second interim analysis,70 deaths were reported: 33 (24%) patients in the brigatinib group had died versus 37 (27%) patients in the crizotinib group.[2] A total of 205 patients were censored: 104 (76%) patients in brigatinib group and 101 (73%) patients in the crizotinib group. The OS data were immature and median OS was not reached in both treatment groups. The Kaplan-Meier curves are presented in Figure 9. The two-year OS rate was 76% (95% CI, 67 – 82%) in the brigatinib group compared to 74% (95% CI, 65 – 80%) in the crizotinib group (HR, 0.92; 95% CI, 0.57 – 1.47; nominal *P* = 0.771).

Figure 9: Kaplan-Meier estimates of OS in the ITT population as of the June 28, 2019 cut-off date



Source: Study 301 IA2 Figure 15.2.5.1.1.1 (data cutoff: 28 June 2019).
ITT: intent to treat; OS: overall survival.

Source: Clinical Summary Report[3]

Camidge et al. (2020)[2] performed an additional sensitivity analysis at the second interim analysis using MSM to adjust for the confounding effects of patient crossover from crizotinib to brigatinib after experiencing progressive disease.[2] In this analysis, the OS HR was 0.70 (95% CI, 0.39 – 1.26) in favour of brigatinib. In addition, IPCW and RPSFTM (with and without re-censoring) analyses were conducted and results were reported in an abstract.[6] These analyses estimated hazard ratios for brigatinib versus crizotinib ranging from 0.446 to 0.939.[6] Most of the methods reduced the HR in favour of brigatinib. Only RPSFTM including re-censoring increased the HR after removing the impact of subsequent brigatinib in the crizotinib group.[6] However, these sensitivity analyses were pre-specified but exploratory, and thus should be interpreted with caution. Interpretation is also limited by the OS data immaturity.

Objective Response Rate

Confirmed ORR by the BIRC was a key secondary outcome in the ALTA-1L trial.[1] As of the February 19, 2018 data cut-off for the first interim analysis, the ORR confirmed by the BIRC was 71% (95% CI, 62 – 78%) in the brigatinib group versus 60% (95% CI, 51 – 68%) in the crizotinib group [odds ratio (OR), 1.59; 95% CI, 0.96 – 2.62; *P* = 0.0678].[1,7] Although the results suggested a trend in favour of brigatinib, they were not statistically significant (P = 0.0678). In the brigatinib group, 4% of patients showed CR whereas 67% showed PR. In the crizotinib group, 5% showed CR whereas 55% showed PR.

As of the June 28, 2019 data cut-off for the second interim analysis, the ORR confirmed by the BIRC was 74% (95% CI, 66 – 81%) in the brigatinib group versus 62% (95% CI, 53 – 70%) in the crizotinib group (OR, 1.73; 95% CI, 1.04 – 2.88; *P* = 0.0342).[2] In the brigatinib group, 15% of patients showed CR and 59% showed PR. In the crizotinib group, 9% showed CR and 53% showed PR. In the exploratory subgroup of patients in the crizotinib group that crossed over to brigatinib (N = 61), the confirmed ORR was 54% (N = 33).[66]

Disease Control Rate

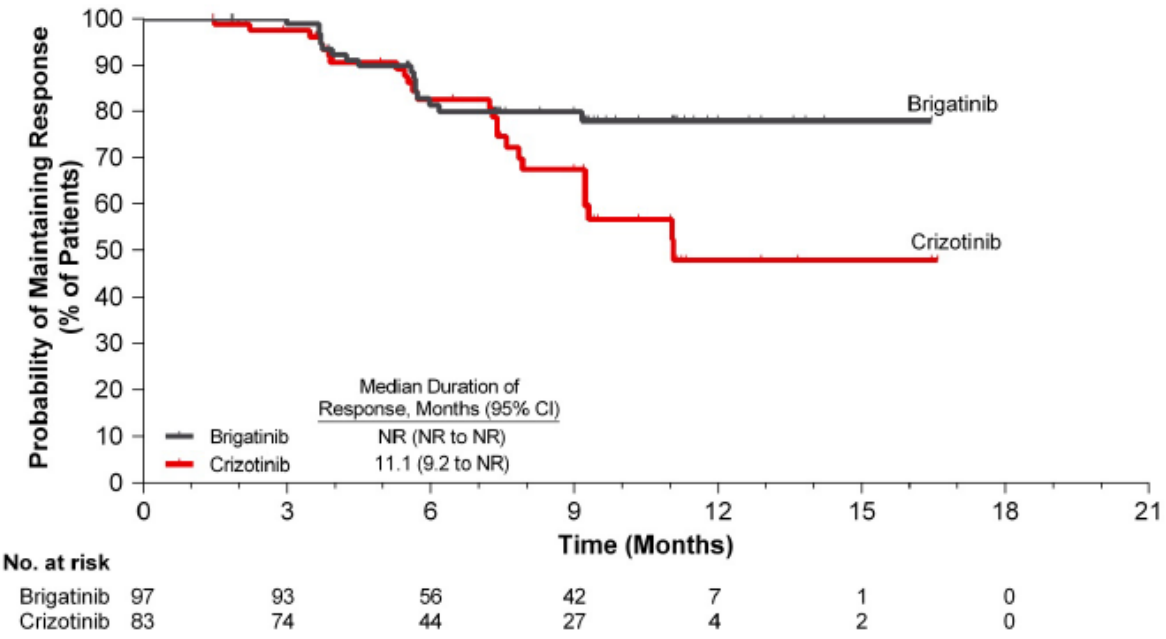
Disease control rate was a secondary outcome in the ALTA-1L trial.[1] As of the February 19, 2018 data cut-off for the first interim analysis, the median DCR was 85% (95% CI, 78 – 90%) versus 86% (95% CI, 79 – 92%) in the brigatinib and crizotinib groups, respectively (OR, 0.93; 95% CI, 0.47 – 1.82; *P* = 0.8220).[7] P value is non-inferential.

As of the June 28, 2019 data cut-off for the second interim analysis, the DCR was 85% (95% CI, 78 – 91%) in the brigatinib group and 86% (95% CI, 79 – 92%) in the crizotinib group (OR, 0.93; 95% CI, 0.47 – 1.82; *P* = 0.8220).[66]

Duration of Response

Duration of response was a secondary outcome in the ALTA-1L trial.[1] As of the February 19, 2018 data cut-off for the first interim analysis, the median DOR was not reached (95% CI, NR – NR) in the brigatinib group versus 11.1 months (95% CI, 9.2 – NR) in the crizotinib group.[1] The Kaplan-Meier curves are presented in Figure 10. The estimated rate of 12-month DOR was 75% (95% CI, 63 – 83%) in the brigatinib group versus 41% (95% CI, 26 – 54%) in the crizotinib group.

Figure 10: Kaplan-Meier estimates of DOR in patients that achieved objective response by the BIRC as of the February 19, 2018 cut-off date



CI = confidence interval; NR = not reached

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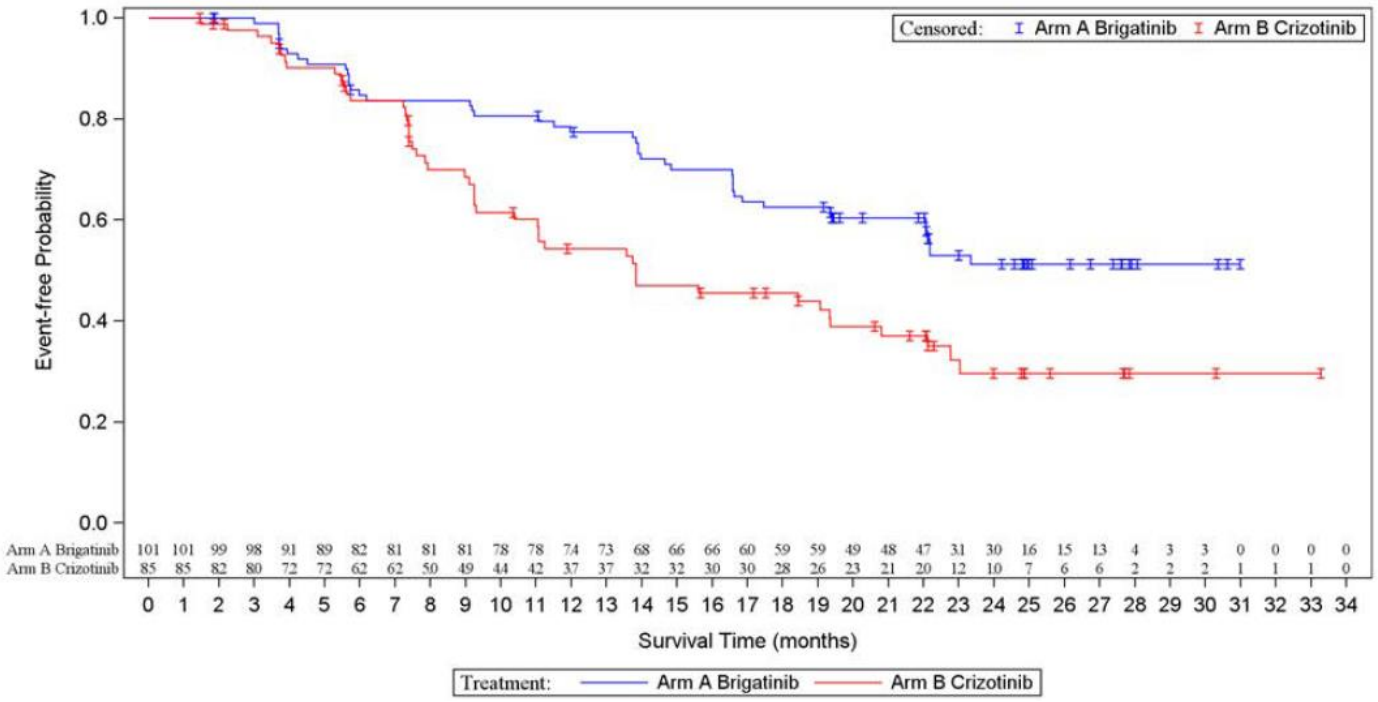
As of the June 28, 2019 data cut-off for the second interim analysis, the median DOR was not reached in the brigatinib group (95% CI, 19.4 months – NR) versus 13.8 months (95% CI, 9.3 – 20.8 months) in the crizotinib group.[2] The 1-year and two-year probabilities of maintaining responses were 77.5% (95% CI, 68 – 85) versus 54.4% (95% CI, 42 - 62) and 51% (95% CI, 40 – 61) versus 30% (95% CI, 18 – 42) in the brigatinib versus the crizotinib groups, respectively.

Figure 11: Kaplan-Meier estimates of DOR in patients that achieved objective response by the BIRC as of the June 28, 2019 data cut-off date



Source: Clinical Study Report[3]

Intracranial Objective Response Rate

Intracranial ORR was a key secondary outcome in the ALTA-1L trial.1 Because the results for confirmed ORR were not statistically significant between study groups, formal statistical testing for iORR was halted and p-values are considered non-inferential and descriptive.

As of the February 19, 2018 data cut-off, 43 patients in the brigatinib group and 47 patients in the crizotinib group had any brain metastases at baseline as determined by the BIRC.[1] In patients with any brain metastases, confirmed intracranial ORR was 67% (N = 29) in the brigatinib group compared to 17% (N = 8) in the crizotinib group (OR, 13.00; 95% CI, 4.38 – 38.61). In the brigatinib group, 37% had complete intracranial response and 30% had partial intracranial response. In the crizotinib group, 4% had complete intracranial response and 13% had partial intracranial response.

As of the June 28, 2019 data cut-off, 47 patients in the brigatinib group and 49 patients in the crizotinib group had any brain metastases at baseline as determined by the BIRC.[2] In patients with any brain metastases at baseline, confirmed intracranial ORR was 66% (95% CI, 51 – 70%) in the brigatinib group versus 16% (95% CI, 7 – 30%) in the crizotinib group (OR, 11.75; 95% CI, 4.19 – 32.91; $P < 0.0001$).

CNS Duration of Response

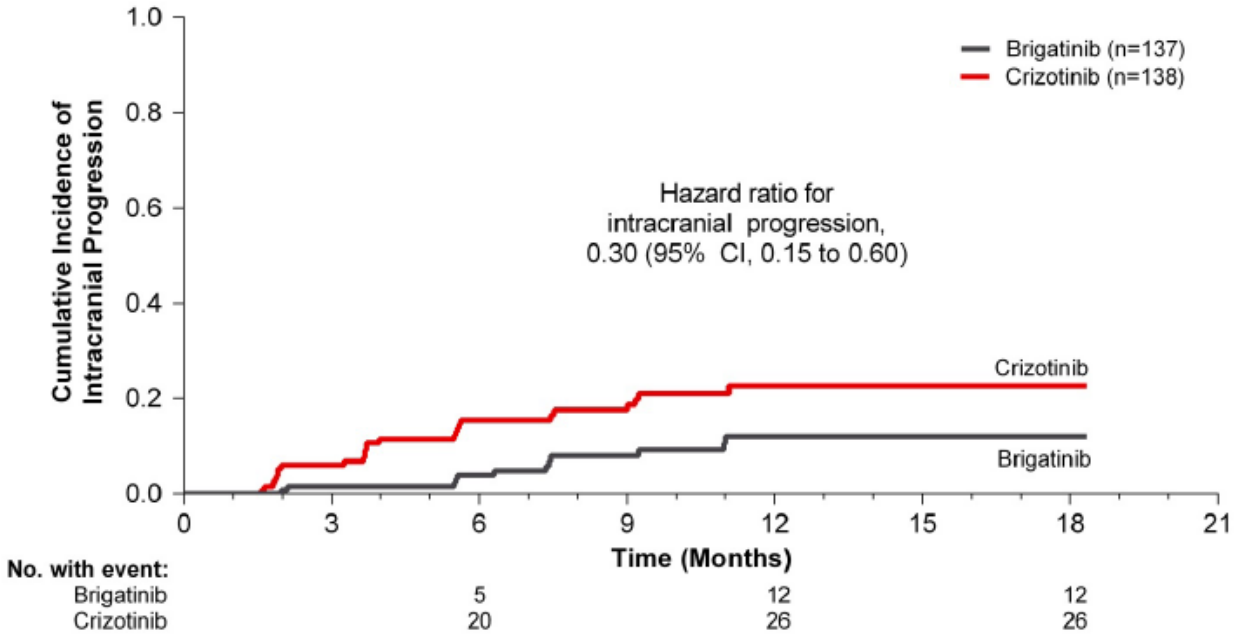
DOR was a secondary outcome in the ALTA-1L trial.[1] As of the February 19, 2018 data cut-off for the first interim analysis, the median intracranial CNS DOR for patients with any brain metastases at baseline was not reached (95% CI, 4.5 – NR) in the brigatinib group compared to 9.2 months (95% CI, 3.9 – 9.2 months) in the crizotinib group.[7]

As of the June 28, 2019 data cut-off for the second interim analysis, the median intracranial CNS DOR was 24.0 months (95% CI, 16.9 months – NR) in the brigatinib group compared to 9.2 months (95% CI, 3.9 months – NR) in the crizotinib group.[2]

Post-hoc analyses: competing risk analyses; time to CNS progression

As of the first interim analysis with a data cut-off of February 19, 2018, 9% (N = 12) of patients in the brigatinib group and 19% (N = 26) of patients in the crizotinib group had intracranial CNS progression as the first site of disease progression (HR, 0.30; 95% CI, 0.15 – 0.60).[1] The cumulative incidence of intracranial CNS progression is presented in Figure 12. The cumulative incidence rate (95% CI) at six months was 4% (2 – 9%) versus 16% (10 – 22%) in the brigatinib and crizotinib groups, respectively.[7] The cumulative incidence rate (95% CI) at 12 months was 12% (6 – 20%) versus 23% (15 – 31%) in the brigatinib and crizotinib groups, respectively.[7] The estimated rate of 12-month survival without intracranial CNS progression in the ITT population was 78% (95% CI, 68 – 85%) in the brigatinib group compared to 61% (95% CI, 50 – 71%) in the crizotinib group (HR, 0.42; 95% CI, 0.24 – 0.70).[1]

Figure 12: Cumulative incidence of intracranial CNS progression in the ITT population as of the February 19, 2018 cut-off date



CI = confidence interval

Source: From the New England Journal of Medicine, Camidge et al, Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, 379, 2027-2039. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

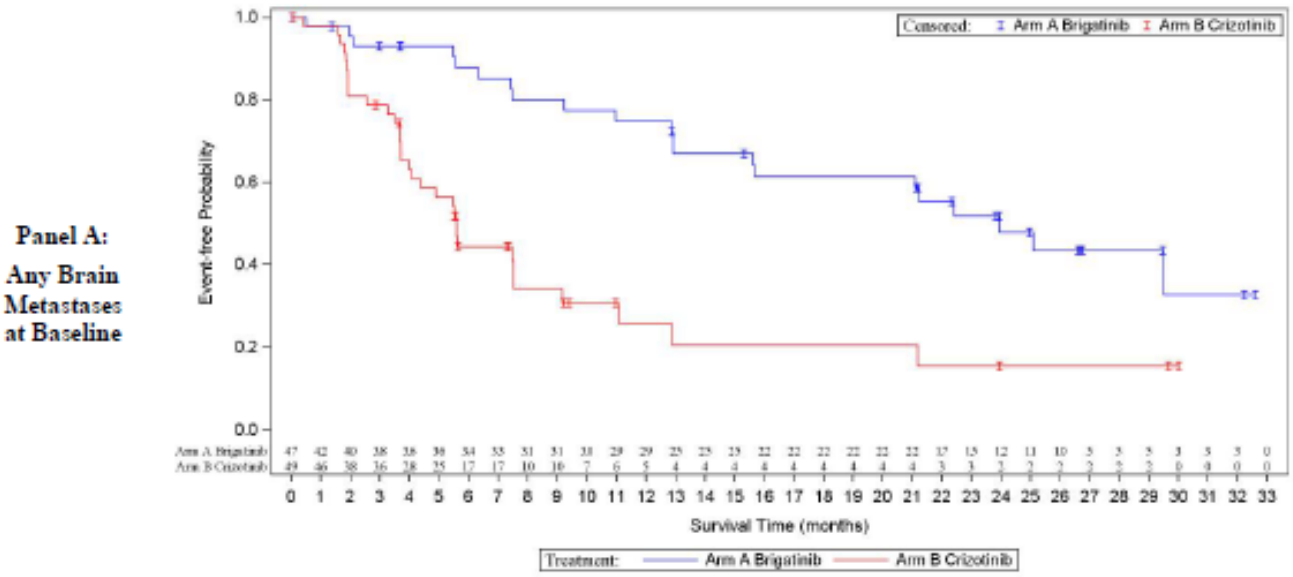
Intracranial PFS

Intracranial PFS was a key secondary outcome in the ALTA-1L trial.[1] Because the results for confirmed ORR were not statistically significant between study groups, formal statistical testing for iPFS was halted and p-values are considered non-inferential and descriptive. As of the first interim analysis, median intracranial PFS in the ITT population was not reached (95% CI, NR – NR) in the brigatinib group versus not reached (95% CI, 11.07 – NR) in the crizotinib group (HR, 0.415; 95% CI, 0.24 – 0.70; *P* = 0.011).[7] In the subgroup of patients with any intracranial CNS metastases at baseline, the median intracranial PFS was not reached (95% CI, 11.0 months – NR) in the brigatinib group compared to 5.6 months (95% CI, 4.1 – 9.2 months) in the crizotinib group (HR, 0.265; 95% CI, 0.13 – 0.54; *P* = 0.0002). In patients without intracranial CNS metastases at baseline, the median intracranial PFS was not reached (95% CI, NR – NR) in both treatment groups.

As of the June 28, 2019 data cut-off for the second interim analysis, 22% (N = 30) of patients in the brigatinib group and 33% (N = 45) in the crizotinib group had intracranial CNS progression.[2] Median intracranial PFS in the ITT population was 32.3 months (95%

CI, 29.5 months – NR) in the brigatinib group compared to 24.0 months (95% CI, 12.9 months – NR) in the crizotinib group (HR, 0.45; 95% CI, 0.29 – 0.69; *P* = 0.0001).[47] In patients with intracranial CNS metastases at baseline, median intracranial PFS as assessed by the BIRC was 24.0 months (95% CI, 12.9 months – NR) in the brigatinib group and 5.6 months (95% CI, 3.7 – 7.5 months) in the crizotinib group. In patients without brain metastases at baseline, median intracranial PFS as assessed by the BIRC was 32.3 months (95% CI, NR – NR) and not reached (95% CI, 24.6 – NR) in the brigatinib and crizotinib groups, respectively. The Kaplan-Meier curves are shown in Figures 13 and 14.

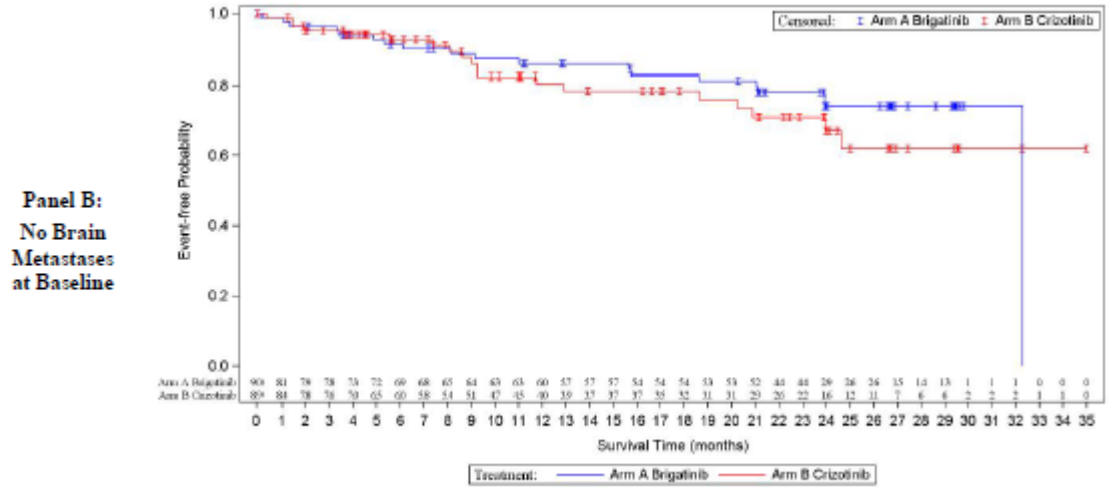
Figure 13: Kaplan-Meier estimates of BIRC-assessed intracranial PFS in patients with intracranial CNS metastases at baseline as of the June 28, 2019 cut-off date



CNS: central nervous system; PFS = progression-free survival, data cutoff: 28 June 2019

Source: Clinical Study Report[3]

Figure 14: Kaplan-Meier estimates of BIRC-assessed intracranial PFS in patients without intracranial CNS metastases at baseline as of the June 28, 2019 cut-off date



Sources: IA2 Figures 15.2.5.1.2.2 and 15.2.5.1.2.4 (data cutoff: 28 June 2019).

CNS: central nervous system, PFS = progression-free survival

Source: Clinical Study Report[3]

Health Related Quality of Life

EORTC QLQ-C30

HRQoL was analyzed in the population of randomized patients with a baseline and ≥ 1 post-baseline HRQoL assessment, which included 131 (96%) patients in the brigatinib group and 131 (95%) patients in the crizotinib group for GHS/QoL by the EORTC QLQ-C30.[2,44]

As of the second interim analysis with a data cut-off of June 28, 2019, overall HRQoL compliance was high in both treatment groups with > 90% of anticipated forms being completed.[44,45] Compliance with EORTC QLQ-C30 assessments over time are summarized in Table 12. Overall EORTC QLQ-C30 compliance across all time points (treatment cycles 1 to 40, end of treatment, and follow-up) was 98% in the brigatinib group and 97% in the crizotinib group.[66] However, compliance was lower at the end of treatment in both the brigatinib (n = 40/56, 71%) and crizotinib groups (n = 32/44, 73%).[66]

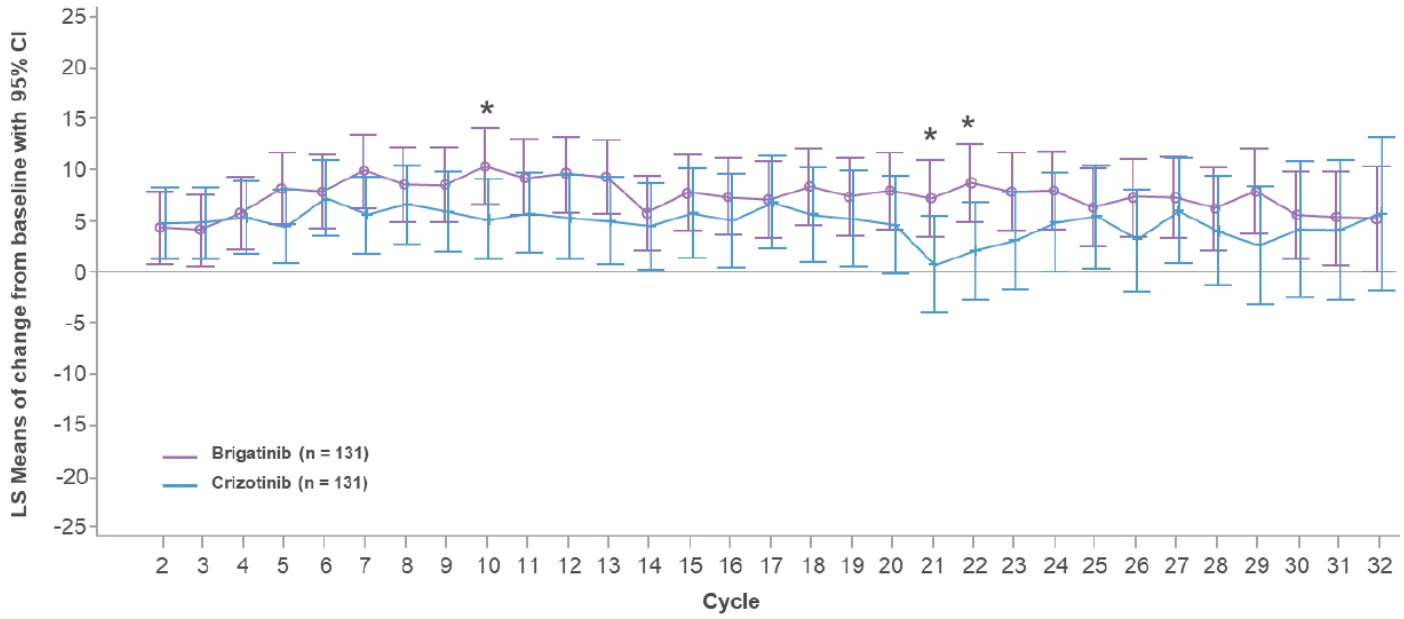
Table 12: Compliance with EORTC QLQ-C30 assessments over time

	Brigatinib N=131		Crizotinib N=131	
Study Visit	Expected n	Received n (%)	Expected n	Received n (%)
Baseline	131	131 (100)	131	131 (100)
Cycle 2 Day 1	123	121 (98.4)	128	125 (97.7)
Cycle 3 Day 1	116	114 (98.3)	124	121 (97.6)
Cycle 4 Day 1	114	111 (97.4)	116	114 (98.3)
Cycle 5 Day 1	112	111 (99.1)	103	101 (98.1)
Cycle 6 Day 1	109	108 (99.1)	96	92 (95.8)
Cycle 7 Day 1	103	102 (99.0)	90	88 (97.8)
Cycle 8 Day 1	103	101 (98.1)	82	81 (98.8)
Cycle 9 Day 1	97	96 (99.0)	76	74 (97.4)
Cycle 10 Day 1	98	98 (100)	69	68 (98.6)
Cycle 11 Day 1	97	94 (96.9)	67	67 (100)
Cycle 12 Day 1	95	95 (100)	59	57 (96.6)
Cycle 13 Day 1	91	91 (100)	55	55 (100)
Cycle 14 Day 1	91	91 (100)	53	53 (100)
Cycle 15 Day 1	90	89 (98.9)	47	46 (97.9)
Cycle 16 Day 1	88	87 (98.9)	41	40 (97.6)
Cycle 17 Day 1	88	85 (96.6)	40	40 (100)
Cycle 18 Day 1	85	83 (97.6)	38	37 (97.4)
Cycle 19 Day 1	82	81 (98.8)	35	35 (100)
Cycle 20 Day 1	83	81 (97.6)	34	34 (100)
Cycle 21 Day 1	82	81 (98.8)	34	34 (100)
Cycle 22 Day 1	82	82 (100)	34	33 (97.1)
Cycle 23 Day 1	81	80 (98.8)	34	34 (100)
Cycle 24 Day 1	81	81 (100)	34	34 (100)
Cycle 25 Day 1	78	78 (100)	31	29 (93.5)
Cycle 26 Day 1	74	74 (100)	30	29 (96.7)
Cycle 27 Day 1	67	66 (98.5)	26	26 (100)
Cycle 28 Day 1	61	61 (100)	23	23 (100)
Cycle 29 Day 1	52	52 (100)	19	19 (100)
Cycle 30 Day 1	45	45 (100)	14	13 (92.9)
Cycle 31 Day 1	37	37 (100)	12	12 (100)
Cycle 32 Day 1	26	26 (100)	10	10 (100)
Cycle 33 Day 1	22	22 (100)	6	4 (66.7)
Cycle 34 Day 1	13	13 (100)	4	4 (100)
Cycle 35 Day 1	10	10 (100)	3	3 (100)
Cycle 36 Day 1	7	7 (100)	2	2 (100)
Cycle 37 Day 1	2	2 (100)	2	2 (100)
Cycle 38 Day 1	1	1 (100)	1	0
Cycle 39 Day 1	1	1 (100)	1	1 (100)
Cycle 40 Day 1	0	0	1	1 (100)
End of Treatment	56	40 (71.4)	73	53 (72.6)
Follow-Up	33	25 (75.8)	44	32 (72.7)
Overall	2907	2854 (98.2)	1922	1857 (96.6)

Source: Response to pCODR checkpoint meeting questions[66]

The mean EORTC QLQ-C30 scores at the second interim analysis are depicted in Figure 15.[3,7] The unadjusted mean was calculated at baseline and the least square (LS) mean (95% CI) was calculated at each cycle. Based on the LS mean difference in change from baseline in EORTC-QLQ-C30 subscale scores, there was a trend for greater improvements in the brigatinib group compared with the crizotinib group with brigatinib showing numerically greater improvements. The estimated mean change differences between the study groups for the GHS/QoL scale ranged from -0.45 (standard error: 2.35) to 6.63 (standard error 2.99) from cycle 2 to cycle 32 with an overall change from baseline in between-group mean difference of 3.1 (95% CI, -0.8 to 7.0). For a plot of LS mean scores over time for the GHS/QoL scale see Figure 15.

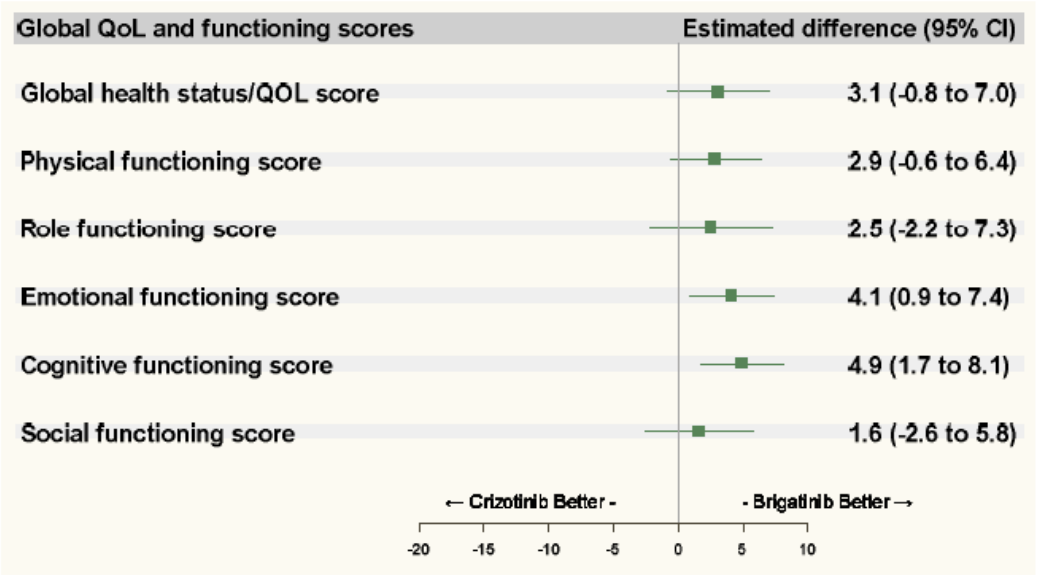
Figure 15: Least squares mean EORTC QLQ-C30 GHS/QOL score from cycle 2 until cycle 32 (4-week cycles) of study treatment in the ALTA-1L trial as of the June 28, 2019 cut-off date.



Source: Clinical Summary[3]

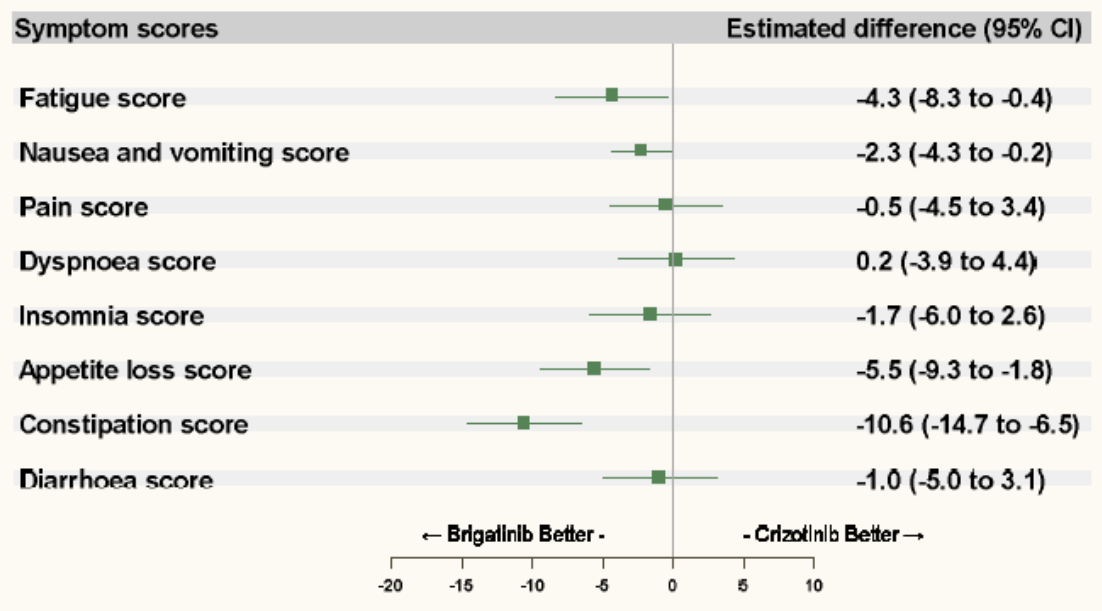
Brigatinib also showed trends towards improvements compared with crizotinib in most functional and symptom subscales of the EORTC QLQ-C30 instrument in between-group mean differences in overall change from baseline (see Figures 16 & 17).

Figure 16: Between-Group Mean Differences in Overall Change from Baseline in EORTC QLQ-C30 Subscale Scores: GHS/QoL and Functioning Scores (PRO-ITT Population)



Source: Clinical Study Report[3]

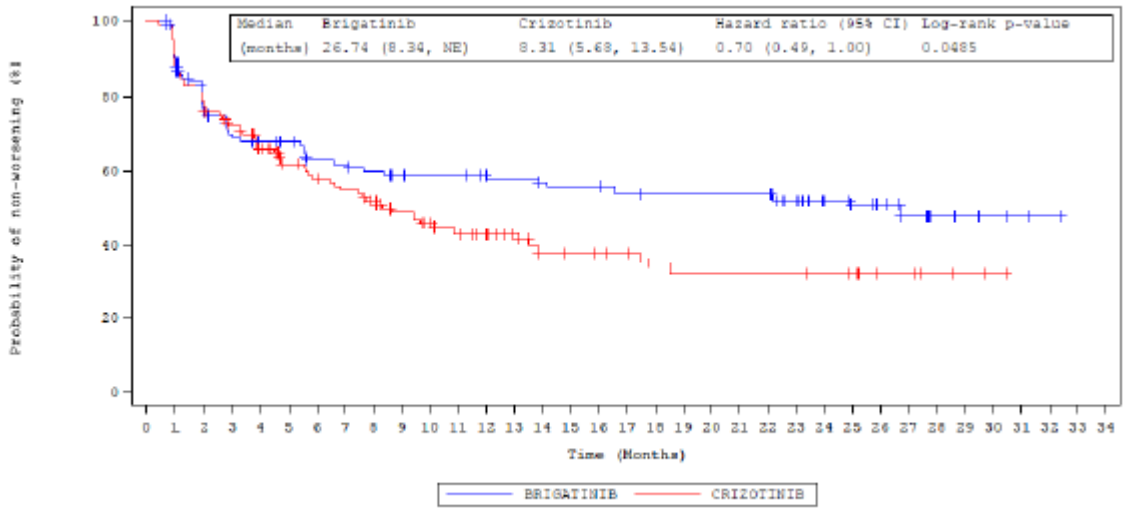
Figure 17: Between-Group Mean Difference in Overall Change from Baseline in EORTC QLQ-C30 Subscale Scores: Symptom Scores (PRO-ITT Population)



Source: Clinical Study Report[3]

The percentage of patients that experienced a worsening event (defined as worsening from baseline of at least 10 points) in the GHS/QoL score from baseline at any time before cross-over was higher in the crizotinib compared to the brigatinib group. As of the second interim analysis, 44% (N = 57) of patients in the brigatinib group and 53% (N = 70) of patients in the crizotinib group had a deterioration in GHS/QoL score of ≥ 10 points;[45] 53% (N = 6) of patients in the brigatinib group and 66% (N = 87) of patients in the crizotinib group had a deterioration of ≥ 8.33 points.[66] Results suggested that brigatinib delayed median time to worsening event compared with crizotinib. The median time to worsening of GHS/QoL score by ≥ 10 points was 26.7 months (95% CI, 8.3 months – NR) and 8.3 months (95% CI, 5.7 – 13.5 months) in the brigatinib and crizotinib groups, respectively (HR, 0.70; 95% CI, 0.49 – 1.00; *P* = 0.049).[2] Median time to worsening of GHS/QoL score by ≥ 8.33 points was 7.5 months (95% CI, 4.7 months – NR) in the brigatinib group and 4.7 months (95% CI, 3.25 – 7.72 months) in the crizotinib group (HR, 0.71; 95% CI, 0.52 – 0.98; *P* = 0.0389).[66] Time to worsening of GHS/QoL score by ≥ 10 points is depicted in Figure 18 and additional data on EORTC QLQ-C30 subscale scores are provided in Table 13. Brigatinib delayed time to worsening event compared with crizotinib across most EORTC QLQ-C30 subscale scores (Table 13).

Figure 18: Time to worsening of GHS/QoL score (≥ 10 points) from the EORTC QLQ-C30 as of the June 28, 2019 cut-off date



Source: IA2 Figure 15.2.9.1.10.3 (data cutoff: 28 June 2019).

Source: Clinical Study Report[3]

Table 13: Time to worsening of EORTC QLQ-C30 subscale scores (≥ 10 points) as of the June 28, 2019 cut-off date

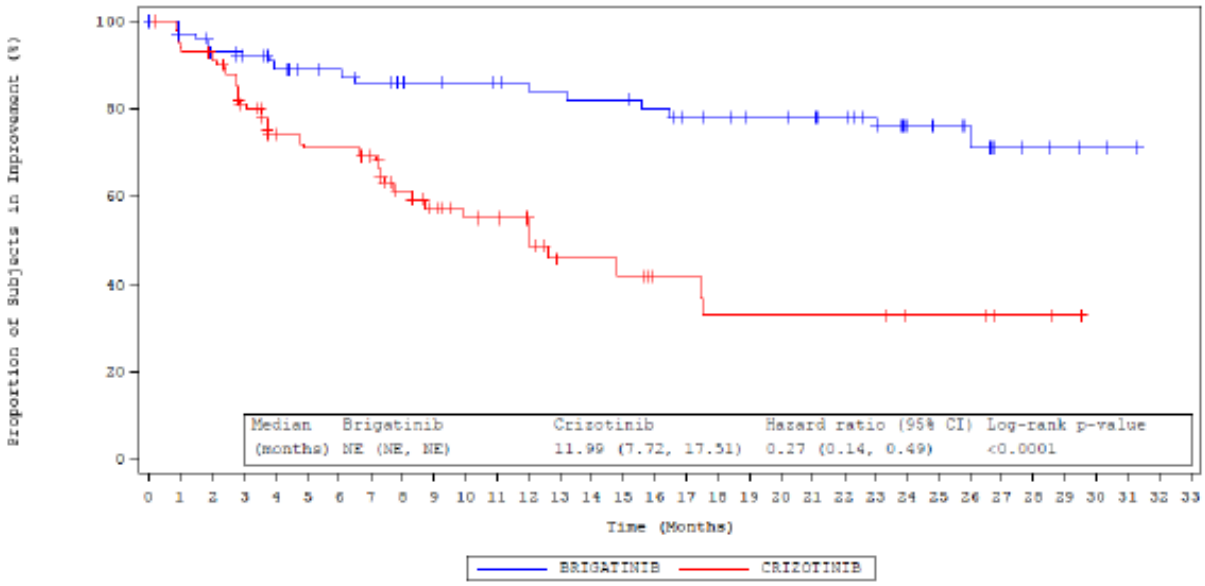
Scores	Median (months) Brigatinib (N = 131)	Median (months) Crizotinib (N = 131)	Hazard Ratio (95% CI)	Log-Rank P-value
Global health status/QoL	26.74 (8.34, NE)	8.31 (5.68, 13.54)	0.70 (0.49, 1.00)	0.0485
Functioning				
Physical functioning	NE (13.86, NE)	10.32 (6.51, 17.54)	0.67 (0.47, 0.97)	0.0505
Role functioning	10.15 (4.30, 21.16)	6.47 (3.88, 9.46)	0.84 (0.61, 1.17)	0.3562
Emotional functioning	NE (22.18, NE)	10.09 (7.62, 14.78)	0.56 (0.38, 0.81)	0.0021
Cognitive functioning	9.30 (4.67, 16.16)	4.47 (3.35, 8.31)	0.75 (0.54, 1.02)	0.0663
Social functioning	27.70 (14.32, NE)	4.76 (2.92, 12.71)	0.59 (0.42, 0.85)	0.0043
Symptoms				
Fatigue	15.64 (7.52, NE)	4.76 (3.25, 8.64)	0.67 (0.48, 0.93)	0.0129
Nausea and vomiting	12.02 (3.98, NE)	2.83 (1.87, 5.59)	0.55 (0.40, 0.76)	0.0002
Pain	12.06 (6.37, 23.20)	8.08 (5.65, 11.63)	0.82 (0.59, 1.15)	0.3008
Dyspnea	28.58 (10.18, NE)	16.76 (10.15, NE)	0.98 (0.67, 1.43)	0.8391
Insomnia	NE (18.63, NE)	22.11 (12.68, NE)	0.91 (0.61, 1.35)	0.7362
Appetite loss	NE (17.48, NE)	9.23 (6.28, 24.90)	0.62 (0.43, 0.90)	0.0092
Constipation	11.99 (6.47, NE)	2.83 (1.87, 3.88)	0.52 (0.38, 0.73)	<0.0001
Diarrhea	2.07 (1.87, 3.75)	2.79 (1.91, 3.75)	1.00 (0.75, 1.34)	0.9682
Financial difficulties	NE (24.94, NE)	NE (19.35, NE)	1.04 (0.67, 1.62)	0.8333

EORTC = European Organization for Research and Treatment of Cancer; NE = not estimable; QLQ = Quality of Life Questionnaire; QoL = quality of life

Source: Clinical Study Report[3]

The percentage of patients with an improvement (defined as an improvement from baseline of 10 points or greater) in the GHS/QoL score was similar between study groups while results suggested a prolonged duration of improvement in the brigatinib compared with the crizotinib group. As of the second interim analysis, 60% (N = 79) of patients in the brigatinib group and 63% (N = 83) of patients in the crizotinib group showed a ≥ 10-point improvement in GHS/QoL score.[3] In patients that demonstrated improvement in GHS/QoL score, the median duration of improvement was not reached in the brigatinib group compared to 12.0 months (95% CI, 7.7 – 17.5 months) in the crizotinib group (HR, 0.27; 95% CI, 0.14 – 0.49; P < 0.0001), as depicted in Figure 19.[2] Duration of improvement was defined as time from the date of first improvement to the date of first occurrence of first deterioration from baseline of at least 10 points after the improvement.[66]

Figure 19: Duration of improvement in GHS/QoL score as of the June 28, 2019 cut-off date

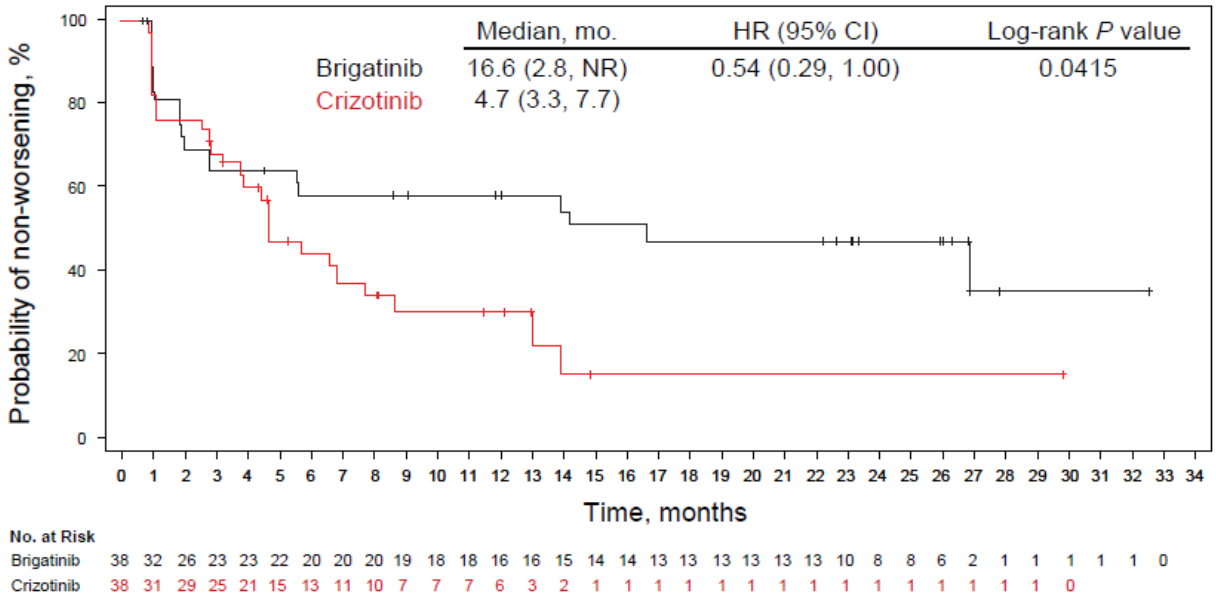


Source: IA2 Figure 15.2.9.1.11 (data cutoff: 28 June 2019).
GHS: global health status; NE: not estimable; QoL: quality of life.

Source: Clinical Study Report[3]

HRQoL data in the CNS metastases subgroups was provided in an abstract.[64] In patients with baseline intracranial CNS metastases, median time to deterioration in GHS/QoL score (≥10 points) was 16.6 months (95% CI, 2.8 months – NR) in the brigatinib group compared to 4.7 months (95% CI, 3.3 – 7.7 months) to the crizotinib group (HR, 0.54; 95% CI, 0.29 – 1.00; *P* = 0.0415) as depicted in Figure 20. In patients without baseline brain metastases, there was no significant difference, as depicted in Figure 21.

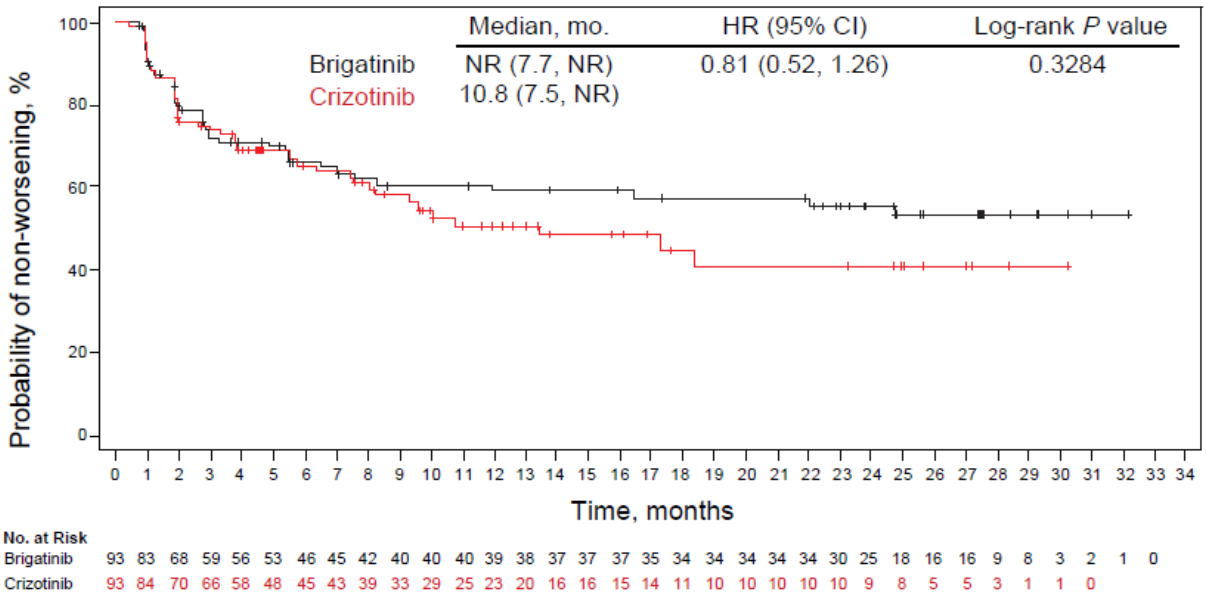
Figure 20: Time to deterioration in GHS/QoL score (≥10 points) from the EORTC QLQ-C30 in patients with intracranial CNS metastases at baseline as of the June 28, 2019 cut-off date



CI = confidence interval; HR = hazard ratio; NR = not reached

Source: Garcia Campelo et al. Poster, European Society for Medical Oncology Virtual Congress, 2020.[63]

Figure 21: Time to deterioration in GHS/QoL score (≥10 points) from the EORTC QLQ-C30 in patients without intracranial CNS metastases at baseline as of the June 28, 2019 cut-off date



CI = confidence interval; HR = hazard ratio; NR = not reached

Source: Garcia Campelo et al. Poster, European Society for Medical Oncology Virtual Congress, 2020.[63]

EORTC QLQ-LC13

The EORTC QLQ-LC13 was added to the ALTA-1L trial in protocol amendment 1, and only patients enrolled after the protocol amendment were included in the analysis.[3] As of the June 28, 2019 data cut-off for the second interim analysis, 63 (46%) patients in the brigatinib group and 78 (57%) patients in the crizotinib group completed the EORTC QLQ-LC13 scale and had a baseline and postbaseline assessment and thus were included in the analysis.[3]

Within the group of patients with EORTC QLQ-LC13 questionnaires completed, overall compliance was 98% in the brigatinib group and 95% in the crizotinib group. The percentage of patients that experienced worsening dyspnea (defined as a 50% decline from baseline) was higher in the crizotinib compared with the brigatinib group. Of the 141 patients, 22% in the brigatinib group and 33% in the crizotinib group experienced worsening dyspnea, (HR, 0.54; 95% CI, 0.28 – 1.04; *P* = 0.0658). Data on median time to worsening of dyspnea are provided in Table 14. The median time to worsening in dyspnea was prolonged in the brigatinib compare with the crizotinib group. Time to worsening was defined as the time from randomization to the first worsening in global health status.[66]

Table 14: Time to worsening of dyspnea by the EORTC QLQ-L13 scale as of June 28, 2019 data cut-off

	Arm A Brigatinib (N = 63)	Arm B Crizotinib (N = 78)
Number with worsening dyspnea (%)	14 (22.2)	26 (33.3)
Number censored (%)	49 (77.8)	52 (66.7)
Time to worsening dyspnea, months		
Median (95% CI)	NE	NE (17.08, NE)
Minimum, maximum	0.85, 31.21	0.43, 31.47
KM estimate, % (95% CI)		
6 months	85 (72, 92)	71 (59, 80)
12 months	77 (63, 86)	67 (54, 77)
18 months	74 (60, 84)	63 (49, 75)
24 months	74 (60, 84)	59 (43, 72)
Log-rank p-value	0.0515	--
HR (95% CI)	0.54 (0.28, 1.04)	--
P-value	0.0658	--

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; NE = not evaluable

Source: Clinical Study Report[3]

Safety Outcomes

Adverse Events

Safety was analyzed in the treated population, which was defined as all patients that received ≥ 1 dose of study drug. The treated population included 136 patients in the brigatinib group and 137 patients in the crizotinib group.[1,2] At both interim analyses, the investigators reported treatment-emergent AEs of any grade that were experienced in ≥ 20% of patients or that differed between treatment groups by ≥ 5%.[1,2] The type of and frequency of AEs were similar at both data cut-offs. AEs as of the second interim analysis (data cut-off June 28, 2019) are presented in Table 15 and found in Table 16.

The number of patients that experienced an any-grade AE was similar in both treatment groups. A greater proportion of patients in the brigatinib group experienced a ≥ grade 3 AE compared to the crizotinib group (73% vs. 61%, respectively). The most commonly reported ≥ grade 3 AEs in the brigatinib group were increased blood creatine phosphokinase (24%), increased lipase (14%), and

hypertension (12%). In the crizotinib group, the most commonly reported ≥ grade 3 AEs were increased ALT (10%), increased AST (7%), and increase lipase (7%).

As of the June 28, 2019 data cut-off, 271 (99.6%) of patients in the treated population had experienced an any-grade AE.[2] The most frequently reported any-grade AEs (brigatinib vs. crizotinib) were diarrhea (52% vs. 56%), nausea (30% vs. 58%), increased blood creatine phosphokinase (46% vs. 17%), cough (35% vs. 20%), increased AST (26% vs. 26%), and increased ALT (21% vs. 35%). In the brigatinib group, 73% (N = 99) experienced a grade ≥ 3 AE compared to 61% (N = 84) in the crizotinib group. The most frequently reported grade ≥ 3 AEs (brigatinib vs. crizotinib) were increased blood creatine phosphokinase (24% vs. 1%), hypertension (12% vs. 3%), increased lipase (14% vs. 7%), and increased ALT (4% vs. 10%).

Treatment-emergent AEs that occurred more frequently in the brigatinib group compared to the crizotinib group included increased blood creatine phosphokinase (44% vs. 15%), increased lipase (22% vs. 12%), increased amylase (18% vs. 7%, respectively), hypertension (17% vs. 2%), pruritus (13% vs. 2%), cough (10% vs. 2%), rash (9% vs. 3%), dermatitis acneiform (7% vs. 2%), and myalgia (6% vs. 0%).[3] Treatment-emergent AEs the occurred less frequently in the brigatinib group compared to the crizotinib group included diarrhea (40% vs. 53%), nausea (23% vs. 50%), peripheral edema (2% vs. 34%), increased ALT (18% vs. 33%), vomiting (9% vs. 30%), constipation (6% vs. 23%), photopsia (0% vs. 20%), visual impairment (0% vs. 17%), dysgeusia (3% vs. 12%), decreased appetite (5% vs. 13%), dizziness (4% vs. 12%), bradycardia (4% vs. 12%), asthenia (7% vs. 12%), increased blood creatinine (2% vs. 10%), upper abdominal pain (2% vs. 10%), decreased neutrophil count (2% vs. 10%), and gastroesophageal reflux disease (0% vs. 5%).[3]

Pulmonary AEs of any grade that occurred in the brigatinib and crizotinib groups included cough (35% vs. 20%), dyspnea (21% vs. 20%), pleural effusion (2% vs. 8%), pulmonary embolism (2% vs. 6%), and interstitial lung disease/pneumonitis (5% vs. 2%).[3] Grade 3 to 4 interstitial lung disease/pneumonitis occurred in 3% (N = 4) of patients in the brigatinib group and 1% (N = 1) of patients in the crizotinib group. Four (3%) patients in the brigatinib group and one (< 1%) patient from the crizotinib group that crossed over to brigatinib experienced early-onset any-grade interstitial lung disease/pneumonitis occurred between day 3 to 8 of brigatinib treatment. No patients receiving crizotinib experienced early-onset interstitial lung disease/pneumonitis.

Table 15: Summary of adverse events in the treated population of ALTA-1L trial as of the June 28, 2019 data cut-off date

	Number of Patients (%)	
	Arm A Brigatinib (N = 136)	Arm B Crizotinib (N = 137)
Patients with TEAEs	135 (99.3)	137 (100.0)
Drug related	124 (91.2)	131 (95.6)
Grade 3 or 4	90 (66.2)	73 (53.3)
Grade 3 or 4, drug related	76 (55.9)	48 (35.0)
Leading to study drug discontinuation	17 (12.5)	12 (8.8)
Leading to dose reduction	52 (38.2)	34 (24.8)
Leading to dose interruption	90 (66.2)	64 (46.7)
Patients with SAEs	45 (33.1)	51 (37.2)
Drug related	16 (11.8)	5 (3.6)
Deaths within 30 days after last dose or possibly related	9 (6.6)	~~11 (8.0)~~10 (7.3)

SAE = serious adverse event; TEAE = treatment-emergent adverse event

Note: The above table was provided as an addendum, including data updated with a correction of a transcription error.

Source: Clinical Study Report[3]

Table 16: Adverse events experienced by ≥ 10% of patients or differed between treatment arms by ≥ 5% in the treated population of ALTA-1L trial as of the June 28, 2019 data cut-off date

	Number of Patients (%)	
Preferred Term	Arm A Brigatinib (N = 136)	Arm B Crizotinib (N = 137)
Patients With Any TEAE	**135 (99.3)**	**137 (100.0)**
Diarrhoea	71 (52.2)	77 (56.2)
Blood Creatine Phosphokinase Increased	63 (46.3)	23 (16.8)
Cough	47 (34.6)	27 (19.7)
Hypertension	43 (31.6)	11 (8.0)
Nausea	41 (30.1)	80 (58.4)
Aspartate Aminotransferase Increased	35 (25.7)	36 (26.3)
Lipase Increased	31 (22.8)	21 (15.3)
Alanine Aminotransferase Increased	29 (21.3)	48 (35.0)
Back Pain	29 (21.3)	23 (16.8)
Headache	29 (21.3)	23 (16.8)
Vomiting	28 (20.6)	60 (43.8)
Dyspnoea	28 (20.6)	28 (20.4)
Fatigue	26 (19.1)	31 (22.6)
Constipation	25 (18.4)	57 (41.6)
Pruritus	25 (18.4)	7 (5.1)
Amylase Increased	24 (17.6)	12 (8.8)
Asthenia	21 (15.4)	26 (19.0)
Dizziness	20 (14.7)	28 (20.4)
Pyrexia	20 (14.7)	21 (15.3)
Rash	20 (14.7)	4 (2.9)
Arthralgia	19 (14.0)	17 (12.4)
Muscle Spasms	19 (14.0)	14 (10.2)
Abdominal Pain	18 (13.2)	20 (14.6)
Blood Alkaline Phosphatase Increased	16 (11.8)	17 (12.4)
Upper Respiratory Tract Infection	16 (11.8)	13 (9.5)
Decreased Appetite	12 (8.8)	26 (19.0)
Dermatitis acneiform	12 (8.8)	3 (2.2)
Dyspepsia	11 (8.1)	22 (16.1)
Bradycardia	11 (8.1)	21 (15.3)
Nasopharyngitis	11 (8.1)	15 (10.9)
Oedema Peripheral	9 (6.6)	61 (44.5)
Blood Cholesterol Increased	9 (6.6)	1 (0.7)
Epistaxis	9 (6.6)	0
Abdominal Pain Upper	8 (5.9)	24 (17.5)
Hypokalaemia	8 (5.9)	1 (0.7)
Rash erythematous	8 (5.9)	1 (0.7)
Hypercholesterolaemia	8 (5.9)	0
Pain In Extremity	7 (5.1)	20 (14.6)
Blood Creatinine Increased	5 (3.7)	20 (14.6)
Dysgeusia	4 (2.9)	19 (13.9)
Dysphagia	3 (2.2)	12 (8.8)
Pleural Effusion	3 (2.2)	11 (8.0)
Neutrophil Count Decreased	2 (1.5)	14 (10.2)
Hypocalcaemia	2 (1.5)	10 (7.3)
Photopsia	1 (0.7)	28 (20.4)
Gastrooesophageal Reflux Disease	1 (0.7)	15 (10.9)
Hypoalbuminaemia	1 (0.7)	10 (7.3)
Hypotension	1 (0.7)	10 (7.3)
Visual Impairment	0	23 (16.8)
Deep vein thrombosis	0	9 (6.6)

Source: IA2 Table 15.3.1.2.1.2 (data cutoff: 28 June 2019).
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment-emergent adverse event.
Patients with 1 or more TEAEs within a level of MedDRA term are counted only once in that level.
MedDRA Dictionary (Version 22.0) was used for coding adverse events.
Treatment-emergent AEs are defined as AEs starting/worsening on or after the first dose of study treatment and no later than the earliest of (1) 30 days after the last dose of the treatment to which the patient was assigned, or (2) the day before start of brigatinib therapy in crossover patients.

Source: Clinical Study Report[3]

Dose interruptions due to AEs occurred in 66% of patients in the brigatinib group and 47% of patients in the crizotinib group.[3] Dose reductions due to AEs occurred in 38% of treated patients in the brigatinib group and 25% of patients in the crizotinib group.[2] AEs leading to dose reductions in the brigatinib group included increased blood creatine phosphokinase (15%), increased lipase (7%), increased amylase (4%), increased AST (2%), hypertension (2%), increased ALT (1%), pneumonitis (1%), and pruritic rash (1%). Treatment discontinuation due to AEs occurred in 13% of patients in the brigatinib group and 9% of patients in the crizotinib group.[2] Treatment emergent AEs leading to treatment discontinuation in more than one patient in the brigatinib group included pneumonitis (2%), pneumonia (2%), bradycardia (2%), and interstitial lung disease (2%).[3] Treatment emergent AEs leading to treatment discontinuation in more than one patient in the crizotinib group included increased ALT (2%) and neoplasm progression (2%).[3] Additional details on treatment emergent AEs leading to study drug discontinuation are presented in Table 17.

Table 17: Adverse events leading to study treatment discontinuation in the ALTA-1L trial as of the June 28, 2019 data cut-off date

	Number of Patients (%)	
System Organ Class Preferred Term	ARM A Brigatinib (N = 136)	ARM B Crizotinib (N = 137)
Patients With At least 1 TEAE Leading to Study Drug Discontinuation	17 (12.5)	12 (8.8)
Infections And Infestations	3 (2.2)	0
Pneumonia	3 (2.2)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (1.5)	3 (2.2)
Diffuse Large B-Cell Lymphoma	1 (0.7)	0
Metastases To Central Nervous System	1 (0.7)	0
Neoplasm Progression	0	2 (1.5)
Hodgkins Disease	0	1 (0.7)
Psychiatric Disorders	1 (0.7)	1 (0.7)
Delirium	1 (0.7)	0
Schizophrenia	0	1 (0.7)
Nervous System Disorders	1 (0.7)	2 (1.5)
Cerebrovascular Accident	1 (0.7)	0
Ischaemic Stroke	0	1 (0.7)
Seizure	0	1 (0.7)
Cardiac Disorders	2 (1.5)	0
Bradycardia	2 (1.5)	0
Respiratory, Thoracic And Mediastinal Disorders	5 (3.7)	2 (1.5)
Pneumonitis	3 (2.2)	1 (0.7)
Interstitial Lung Disease	2 (1.5)	0
Respiratory Failure	0	1 (0.7)
Gastrointestinal Disorders	1 (0.7)	2 (1.5)
Dysphagia	1 (0.7)	0
Diarrhoea	0	1 (0.7)
Nausea	0	1 (0.7)
Skin And Subcutaneous Tissue Disorders	1 (0.7)	0
Rash Pruritic	1 (0.7)	0
Investigations	1 (0.7)	3 (2.2)
Alanine Aminotransferase Increased	1 (0.7)	3 (2.2)
Aspartate Aminotransferase Increased	1 (0.7)	1 (0.7)
Blood Alkaline Phosphatase Increased	1 (0.7)	0
Blood Bilirubin Increased	0	1 (0.7)

TEAE = treatment-emergent adverse event

Source: Clinical Study Report[3]

Serious Adverse Events

As of the June 28, 2019 data cut-off, 33% (N = 45) of patients in the brigatinib group and 37% (N = 51) in the crizotinib group experienced serious adverse events (SAEs).[3] Drug-related SAEs occurred in 12% (N = 16) and 4% (N = 5) of patients in the brigatinib and crizotinib groups, respectively. SAEs of grade 3 or 4 occurred in 22% of patients in both the brigatinib and crizotinib groups.

During the period of randomized treatment and survival follow-up, 24% of patients in the brigatinib group and 18% of patients in crizotinib group died. The most common reason for death was cancer-related (20% and 14% in the brigatinib and crizotinib groups, respectively). Adverse events resulting in death within 30 days of the last study drug dose occurred in 7% (N = 9) of patients in the brigatinib and 7% (N = 10) of patients in the crizotinib group. All AEs resulting in death were assessed as unrelated to the study drug.

Withdrawals due to Adverse Events

The sponsor did not collect data on patient withdrawals specifically due to AEs.[66] As of the June 28, 2019 data cut-off, 14 (10%) patients in the brigatinib group and 5 (4%) in the crizotinib group withdrew consent during the ALTA-1L trial.[2] In addition, 13% of patients in the brigatinib group and 9% of patients in the crizotinib group discontinued their assigned treatment due to AEs.[2]

6.4 Ongoing Trials

One ongoing trial was identified as relevant to this review and may provide future insights on using brigatinib versus alectinib in the first line setting for ALK-positive locally advanced or metastatic NSCLC. The study is an open-label, randomized phase II trial being conducted at multiple centres in Germany in adult patients with stage III and IV ALK-positive NSCLC. The objectives of the trial are to compare the efficacy of brigatinib to other second-generation ALK inhibitors (i.e., ceritinib and alectinib) in the first- and second-line setting, and to explore treatment resistance patterns related to tumor's molecular characteristics. Additional details on this ongoing trial are provided in Table 18.

Table 18: Ongoing trials of brigatinib in ALK-positive locally advanced or metastatic NSCLC

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study Advancing Brigatinib Properties in Anaplastic Lymphoma Kinase Positive Non-Small Cell Lung Cancer (ALK+ NSCLC) Patients by Deep Phenotyping[69] ClinicalTrials.gov Identifier: NCT04318938 EudraCT Number: 2019-001828-36 **Characteristics** Phase II, open-label, randomized active-controlled trial Estimated N randomized = 116 **Number of Centres and Countries** 18 centres in Germany **Patient Enrolment Dates**	Key Inclusion Criteria: • Adults ≥ 18 years old • Histologically confirmed locally advanced (stage III) and not suitable for curative treatment or metastatic (stage IV) ALK-positive NSCLC • No prior therapy for metastatic ALK-positive NSCLC including ALK inhibitors (1-2 cycles of chemotherapy and cerebral irradiation allowed) • ≥ 1 measurable lesion per RECIST version 1.1 • ECOG performance status ≤ 2 • Adequate organ function Key Exclusion Criteria: • History or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis • Uncontrolled hypertension	First-line: Brigatinib 90 mg orally once daily for 7 days then 180 mg orally once daily Second-line: Investigator's choice of alectinib or ceritinib *versus* First line: Investigator's choice of alectinib or ceritinib Second-line: Investigator's choice of alectinib, ceritinib, or brigatinib	Primary: • PFS of first-line treatment Secondary: • PFS of second-line treatment • TNT of first-line treatment • TNT of second-line treatment • TNT for first and second-line treatments together • OS • Intracranial ORR • Intracranial DOR • Time to intracranial progression • Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study Start Date: March 30, 2020 Estimated Completion Date: December 31, 2025 **Final Analysis Date** Trial is ongoing with an estimated completion date of December 31, 2025. **Sponsor** Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest (Institute of Clinical Cancer Research IKF at Nordwest Hospital) **Funding** Takeda Pharmaceutical Company Ltd	• Treatment with CYP3A inducers or inhibitors, chemotherapy, or radiation therapy (except for radiosurgery or stereotactic body radiation therapy) within 14 days of randomization • Treatment with antineoplastic monoclonal antibodies within 30 days of randomization • Major surgery within 30 days of randomization • Spinal cord compression • Significant or uncontrolled CVD • Cerebrovascular accident or TIA within 6 months of first dose of study drug • Malabsorption syndrome or GI disorder affecting oral absorption of drugs • Pregnant or breastfeeding		• HRQoL (SF-12 and EORTC-QLQ-BN20) Exploratory: • ALK fusion variants in tumor tissue, blood samples, and CSF • TP53 mutation status in tumor tissue, blood samples, and CSF • Acquired resistance mutations via standardized next-generation sequencing-based multiplex analysis in tumor tissue, blood samples, and CSF • Efficacy according to ALK fusion variant and TP53 status • Molecular resistance patterns after first-line treatment failure • Impact of second-line treatment • Clinical utility of CSF circulating tumor DNA analysis in intracranial CNS disease progression

ALK = anaplastic lymphoma kinase; CNS = central nervous system; CSF = cerebrospinal fluid; CVD = cardiovascular disease; DOR = duration of response; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ= European Organization for Research and Treatment of Cancer quality of life questionnaire; GI = gastrointestinal ; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TIA = transient ischemic attack; TKI = tyrosine kinase inhibitor; TNT = time-to-next-treatment; TP53 = tumor protein p53

7 Supplemental Questions

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of brigatinib for ALK+ NSCLC:

- Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison Using Matched Adjusted Indirect Comparison
- Critical Appraisal of the Elliott et al.[12] Published Indirect Treatment Comparison Using Network Meta-Analysis
- Critical Appraisal of the Ando et al.[13] Published Indirect Treatment Comparison Using Network Meta-Analysis

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

7.1 Critical Appraisal of the Sponsor-Submitted Indirect Treatment Comparison Using Matched Adjusted Indirect Comparison

7.1.1 Objective

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. Consequently, the sponsor provided indirect treatment comparisons (ITCs) using matched adjusted indirect comparisons (MAICs) and the Bucher ITC method of relevant comparators, which were identified based on a systematic review of treatments for locally advanced or metastatic ALK+ NSCLC.[8] The focus of the ITCs was to compare 1) brigatinib and alectinib via MAICs (both anchored and unanchored) and the Bucher ITC method (including the ALTA-1L[9] and ALEX[4] trials) and 2) brigatinib and ceritinib via MAICs (including the ALTA-1L[9] and ASCEND-4[25] trials).

7.1.2 Findings

A single sponsor's submitted multiple ITCs, which have been described and critically appraised in the sections below.

Methods

Systematic review

The systematic review that was submitted by the sponsor was conducted to identify data on relevant comparators included in the ITC. The review was based on searches of MEDLINE, Embase, Cochrane Library, PubMed, and Web of Science that were conducted in May 2018 with updates in May 2019 and additionally in January 2020. In addition, clinical trial registries, conference proceedings (from 2015 onwards), and regulatory and HTA websites were searched. Reference lists of clinical practice guidelines, review articles, and relevant studies were scanned to identify additional potentially relevant studies.

The eligibility criteria for the systematic review were published reports of ALK inhibitors (brigatinib, ceritinib, crizotinib, alectinib, ensartinib, loratinib) for ALK-inhibitor naïve adult patients aged 18 years or older with locally advanced or metastatic ALK+ NSCLC. Prospective intervention trials were included if they were randomized controlled trials (RCTs), non-RCTs, as well as single group trials. Studies published in any language or in any year were included. Studies were excluded if they included patients <18 years of age, focused on SCLC, did not confirm ALK rearrangements, patients received >1 prior systemic therapy for advanced disease, patients received previous TKI treatment, did not examine a relevant intervention, did not report eligible outcomes, and were not relevant study designs (e.g., non-systematic reviews, expert opinion, letters, editorials, press releases, case studies, preclinical studies). The inclusion criteria are outlined in Table 19.

Table 19: PICOS Eligibility Criteria

PICOS Item	Eligibility Criteria
Population	Adults aged ≥18 years with locally advanced or metastatic ALK+ NSCLC who were treatment naïve or one previous systemic anticancer treatment and TKI-naive
Interventions	The following alone or in combination:

PICOS Item	Eligibility Criteria
	Brigatinib Crizotinib Ceritinib Alectinib Ensartinib Lorlatinib
Comparators	Any comparator, including single group trials without a comparator
Outcomes	Efficacy outcomes: • Progression-free survival (PFS) • Overall survival (OS) • Objective response rate (ORR) • Duration of response (DOR) • Disease control rate (DCR) • Time to response (TTR) • Intracranial response rate (IC-RR) • Intracranial progression-free survival • Intracranial duration of response Harms outcomes: • All-grade AEs • Grade 3 or 4 AEs • Discontinuation due to AEs • Dose reduction due to AEs • Early-onset pulmonary event (EOPE) • All-cause mortality Patient reported outcomes: • EORTC QLQ C-30 • EORTC QLQ-LC13 • EQ-5D
Study design	Randomized controlled trials, (RCTs) open-label trials, crossover trials, non-randomized comparative trials, single-arm prospective trials, observational trials, systematic reviews, guidelines, abstracts

Source: Sponsor submitted MAIC[8]

AEs = adverse events; ALK+ = anaplastic lymphoma kinase positive; DCR = disease control rate; DOR = duration of response; EOPE = early onset pulmonary event; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-LC13= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; EQ-5D = EuroQol 5-dimension; IC-RR = intracranial response rate; NSCLC = non-small cell lunch cancer; ORR = objective response rate; OS = overall survival; PFS = progression free survival; RCT = randomized controlled trials; TKI = tyrosine kinase inhibitor; TTR = time to response.

Regarding the conduct of the systematic review, study selection was conducted by two independent reviewers in the Covidence software,[70] with disagreements resolved by a third reviewer.[8] Data were abstracted by two independent reviewers in Excel, with disagreements resolved by a third reviewer.[70] Two reviewers conducted risk of bias appraisal using the Cochrane risk of bias tool, with discrepancies resolved through discussion or a third reviewer.[70]

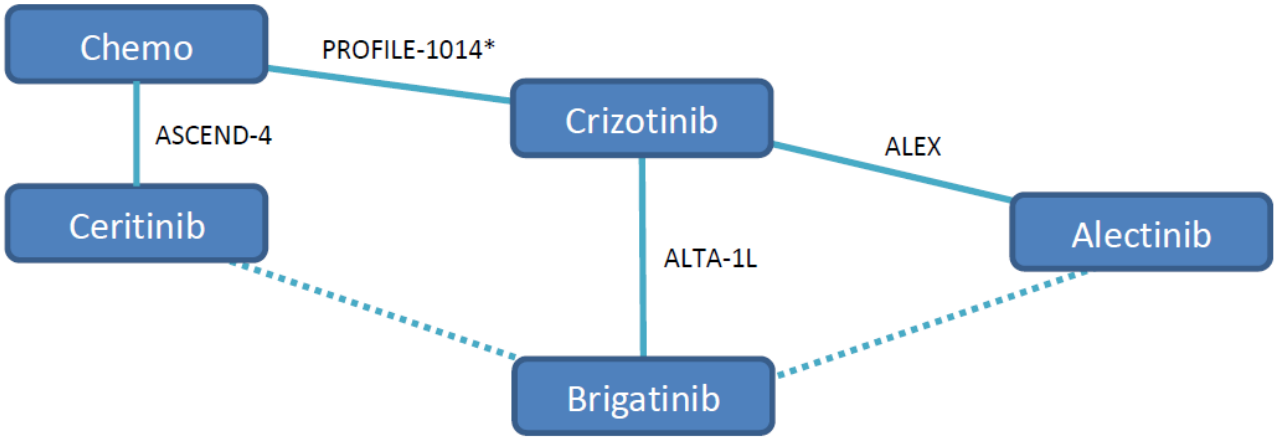
Methods for indirect treatment comparisons[8]

Two treatment comparisons were included by the sponsor's ITCs: brigatinib versus alectinib and brigatinib versus ceritinib (Figure 22). For the former, NMA was not deemed feasible by the sponsor, as there were differences in the ALTA-1L and ALEX trials due to treatment switching and imbalances in baseline brain metastases. For the latter comparison, the NMA was not deemed feasible because the chemotherapy groups in the PROFILE-1014 and ASCEND-4 trials were not comparable. For the brigatinib versus alectinib comparison, the Bucher ITC approach, which anchors the indirect comparison to a common comparator, preserving the randomization of the trials included in the analysis, was conducted including the ALTA-1L and ALEX trials. The Bucher ITC approach uses aggregate data and does not use IPD. Since treatment switching occurred much more frequently in ALTA-1L than in ALEX, an anchored MAIC was also considered for the brigatinib versus alectinib treatment comparison, as the sponsor noted that the crizotinib

group of the ALTA-1L trial may have a greater likelihood of more favourable OS than the crizotinib group of ALEX due to treatment switching. For the brigatinib versus ceritinib comparison, differences were noted by the sponsor between chemotherapy groups of PROFILE-1014 and ASCEND-4, and as such, the only remaining option was to conduct an unanchored MAIC based on the results of ALTA-1L and ASCEND-4. For unanchored MAIC, no methods were used to check residual confounding, as the sponsor noted that the results for anchored and unanchored MAICs were similar for the PFS, ORR, and DOR outcomes, indicating a low likelihood of residual bias.[66]

Figure 22: Network Geometry

Figure 3.2: Evidence Network for First-line Treatment of ALK+ NSCLC



Note: Solid lines represent direct comparisons and dotted lines represent indirect comparisons.
* PROFILE 1007 was not considered for inclusion in the network since the chemotherapy comparator in this trial (i.e., pemetrexed or docetaxel) was not compatible with the chemotherapy comparator in ASCEND-4. PROFILE 1029 was not considered since it exclusively enrolled an East Asian population.

Source: Sponsor submitted MAIC[8]

The sponsor noted that the variables selected for matching in MAIC were identified using a variety of methods (presented here in no preferential order); considering what IPD was available from the ALTA-1L trial, using previous NICE submissions, and expert opinion. The seven candidate variables from all of these sources included sex, age (65+ years versus not), smoking status, ethnicity (Asian versus non-Asian), baseline brain CNS metastases status, ECOG PS (0/1 versus 2), and having received one prior chemotherapy regimen. According to experts, these prognostic variables were considered for all the MAICs.[8] The sponsor noted that this list was validated by clinicians at a January 2020 clinical advisory board as containing all variables which may impact prognosis and/or the treatment effect. Additionally, this list was exhaustive following a review of alectinib submission dossiers and brigatinib second-line dossiers according to the sponsor. The MAIC was conducted using the shared effect modifier assumption, which means that the ITC results can be applied to any target population. To determine whether the variables were indeed effect modifiers, Cox proportional hazards models were run for each variable using IPD from the ALTA-1L trial.[66] The size of the interaction coefficient and respective confidence interval or p-value was used to determine whether the variable was an effect modifier or not. Based on these results, the anchored MAICs were adjusted for baseline brain CNS metastases only. The sponsor noted that at a later advisory board, the results of these analyses were presented, and clinicians agreed that this made sense and that they would only expect baseline CNS metastases to be treatment effect modifying when comparing to crizotinib; there was a unanimous belief that this factor was no longer treatment effect modifying with the later generation ALK inhibitors i.e. brigatinib and alectinib.[66] The sponsor reported that clinicians were further asked whether any variable was missing from the analysis – it was confirmed that this list was exhaustive.[66] The unanchored MAICs were adjusted for age, sex, smoking status, if the patient was Asian, baseline brain CNS metastases, ECOG PS score 2, and treatment with one prior chemotherapy (the latter variable was not adjusted for in the unanchored MAIC for brigatinib

versus alectinib, as this variable was not reported in the ALEX trial[4]). The ALTA-1L trial had data on all seven MAIC covariates, the ALEX trial had data on six of the seven covariates (receipt of prior chemotherapy was missing) and ASCEND-4 had data on all seven covariates (Figure 23).

Figure 23: Availability of MAIC Covariates

Table 3.10: Availability of MAIC Covariates

	Brigatinib	Alectinib	Ceritinib
	ALTA-1L[16]	ALEX[23]	ASCEND-4[26]
ECOG PS	✓	✓	✓
Brain metastases	✓	✓	✓
Age	✓	✓	✓
Gender	✓	✓	✓
Smoking status	✓	✓	✓
Receipt of any prior chemotherapy	✓	×	✓
Ethnicity	✓	✓	✓

Abbreviations: ECOG PS = European Cooperative Oncology Group Performance Status.

Source: Sponsor submitted MAIC[8]

For the analysis, to estimate the parameters of the model in the MAIC, a method of moments approach was used. Subsequently, these weights were used to generate an adjusted Kaplan-Meier curve, permitting estimation of the HRs between each comparator versus brigatinib for the OS, PFS, and DOR outcomes. For these time-to-event outcomes, the proportional hazards assumption was tested by comparing log (cumulative hazards) versus log (time) plots, as well as the assessing Schoenfeld plots and the respective p values. It was concluded that the proportional hazards assumption was likely upheld.[66] The MAIC weights were also used to estimate the odds ratio (OR) using logistic regression for the ORR outcome. The ORR outcome was investigator-assessed and patients with missing information were excluded from the MAIC. The effective sample size (ESS) was used to estimate the number of individuals that would be required to give an estimate with the same level of precision as that from the weighted sample. The more variables that the trial populations are being matched on, the smaller the ESS may become. The ESS was reported for all analyses, including demographics before and after weighting. The sponsor noted that the brigatinib group from the ALTA-1L trial was compared against the alectinib group from the ALEX trial.[66] In this comparison, the crizotinib groups were not used as a linking treatment for an ITC and the ESS statistic is only applicable to brigatinib and alectinib. As such, the ESS was not calculated for the crizotinib group. In addition, the range of weights applied to each patient in the MAIC analysis for each outcome were provided. Clinical heterogeneity was examined by the sponsor by comparing the trials with respect to their eligibility criteria, baseline characteristics, duration of follow-up, and outcome assessment. All MAICs were conducted in the R statistical software version 3.61 and above.

In the ALTA-1L trial, 44.5% of patients in the crizotinib group switched to brigatinib after documented disease progression or radiotherapy to the brain and an additional 23 patients switched based on their medical records (8.8% switched from crizotinib to brigatinib and 8.1% switched from brigatinib to crizotinib). The sponsor noted that this likely biased the results, and as such, statistical adjustments were attempted using the RPSFTM. This model allows the estimation of survival times that would have been observed had switching not occurred. To examine the robustness of results, several variations for the RPSFTM analyses were conducted: switch pool (official switchers versus all switchers [12 patients in the crizotinib group unofficially switched to brigatinib or used brigatinib as subsequent therapy after end of study]), censoring (yes or no), confidence interval method (bootstrap or standard), analyses that did not adjust for treatment switching, and anchored MAICs and Bucher ITC were conducted using both treatment switch-adjusted and unadjusted results from ALTA-1L (for the OS outcome only). The RPSFTM analyses were conducted at different time points, as the outcomes were assessed at different times.[8]

For the ITCs, only a single group was selected for each trial. For the brigatinib versus alectinib analysis, the brigatinib group was from the ALTA-1L trial and the alectinib group was from the ALEX trial. For the brigatinib versus ceritinib analysis, the brigatinib group was from the ALTA-1L trial and the ceritinib group was from the ASCEND-4 trial.

For the ITCs, the outcomes of interest were as follows:[8]

- Overall Survival (OS)
- Objective/Overall Response Rate (ORR): Investigator unconfirmed or investigator confirmed
- Progression-Free Survival (PFS): Measured using investigator assessment (INV) and/or a blind independent review committee (BIRC)
- Duration of Response (DOR): Based on investigator unconfirmed response

Results

Systematic review results and NMA feasibility assessment

Overall, 185 unique records were identified, and 18 studies were included. Eight studies were RCTs and the rest were non-RCTs. The included studies examined the following interventions: brigatinib (n= 1 RCT), alectinib (n= 3 RCTs, 1 non-RCT, 1 trial of concomitant interventions that the sponsor referred to as “combination trials”), ceritinib (n= 1 RCT, 3 non-RCTs), crizotinib (n= 3 RCTs, 2 non-RCTs, 2 combination trials), and lorlatinib (1 non-RCT). Of the included trials, only ALTA-1L and ASCEND-4 were phase III RCTs examining brigatinib and ceritinib. For alectinib, although 3 phase III RCTs were available, two were excluded, as they were conducted exclusively in Japanese patients, and as such, only the ALEX trial was selected for this intervention. Overall, three RCTs were included in the ITCs: ALTA-1L, ALEX, and ASCEND-4.[8]

Trial characteristics

The detailed inclusion criteria for the three RCTs included in the Bucher ITC and MAICs are provided in Table 20. The RCTs had similar inclusion and exclusion criteria. All three included histologically or cytologically confirmed advanced ALK+ NSCLC with measurable disease according to the RECIST criteria (version 1.1). Patients had ECOG PS 0-2 (in ALTA-1L and ALEX) or WHO PS 0-2 (ASCEND-4) and were aged 18 years and older. The inclusion criteria were similar across the trials.[8]

Table 20: Eligibility Criteria for the Included Trials

Intervention	Trial	Inclusion Criteria	Exclusion Criteria
Brigatinib	ALTA-1L	Histologically or cytologically confirmed stage IIIB (and not a candidate for definitive multimodality therapy) or stage IV NSCLC; Documented ALK rearrangement; Sufficient tumor tissue available for central analysis; At least 1 measurable (i.e., target) lesion per RECIST v1.1;	Previously received an investigational antineoplastic agent for NSCLC; Previously received any prior TKI, including ALK-targeted TKIs; Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease;

Intervention	Trial	Inclusion Criteria	Exclusion Criteria
		Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade ≤ 1; ≥18 years old; Adequate organ function; ECOG PS ≤ 2; Normal QT interval on screening ECG evaluation, defined as QT interval corrected (Fridericia) (QTcF) of ≤ 450 msec in males or ≤470 msec in females; For female patients of childbearing potential, have a negative pregnancy test documented prior to randomization; For female and male patients who are fertile, agree to use a highly effective form of contraception, as defined by the study protocol; Provide signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating; Have the willingness and ability to comply with scheduled visit and study procedures.	Received chemotherapy or radiation within 14 days of first dose of study drug; Received anti-neoplastic monoclonal antibodies or had major surgery within 30 days; Diagnosed with another primary malignancy other than NSCLC; Symptomatic CNS metastases.
Ceritinib	ASCEND-4	18 years or older; Histologically or cytologically confirmed locally advanced or metastatic non-squamous ALK-rearranged NSCLC untreated with any systemic anticancer therapy (ALK-rearrangement was determined centrally by the VENTANA anti-ALK (D5F3) immunohistochemistry assay; Measurable disease as per RECIST 1.1 criteria; WHO performance status 0–2; Asymptomatic or neurologically stable brain metastases (for ≥ 2 weeks); Previous radiotherapy to the brain must have been completed at least 2 weeks before the start of ceritinib treatment.	Known hypersensitivity to any of the excipients of ceritinib; History of severe hypersensitivity reaction to platinum-containing drugs, pemetrexed, or any known excipients of these drugs; History of interstitial lung disease or interstitial pneumonitis; History of carcinomatous meningitis; A concurrent malignancy or history of a malignant disease other than NSCLC that had been diagnosed or required therapy within the past 3 years; clinically significant, uncontrolled heart disease, or recent cardiac event (within 6 months); Impairment of GI function or GI disease that could substantially alter the absorption of ceritinib; Patients who received thoracic radiotherapy to lung fields 4 weeks or less before starting the study treatment or patients who had not recovered from radiotherapy-related toxicities; • Those who underwent major surgery within 4 weeks before (2 weeks for resection of brain metastases) starting study treatment or had not recovered from side-effects of such procedure.
Alectinib	ALEX	Histologically or cytologically confirmed advanced NSCLC that was ALK positive by VENTANA ALK (D5F3) immunohistochemical assay conducted at central laboratories; 18 years of age or older; ECOG PS of 0 to 2; No previous systemic treatment for advanced NSCLC;	Patients with a previous malignancy within the past 3 years; Any GI disorder or liver disease; NCI CTCAE (version 4.0) Grade 3 or higher toxicities due to any prior therapy (e.g. radiotherapy); History of organ transplant;

Intervention	Trial	Inclusion Criteria	Exclusion Criteria
		Measurable disease (according to RECIST version 1.1); Adequate hepatic, renal, and bone marrow function.	Co-administration of anti-cancer therapies other than those administered in this study; • Baseline QTc > 470 ms or patients with symptomatic bradycardia < 45 beats per minute; Administration of strong/potent cytochrome P450 (CYP)3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib or crizotinib; Administration of agents with potential QT interval prolonging effects within 14 days prior to the first administration of study drug and while on treatment; History of hypersensitivity to any of the additives in the alectinib and/or crizotinib drug formulation; Pregnant or lactating women; Known HIV positivity or AIDS-related illness; Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study; • Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry.

Source: pCODR Submission[8]

AIDs = acquired immunodeficiency syndrome; ALK = anaplastic lymphoma kinase; CNS = central nervous system; ECG = electrocardiogram; ECO = Eastern Cooperative Oncology; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in-situ hybridization; GI = gastrointestinal; HIV = human immunodeficiency virus; IHC = immunohistochemistry; IMP = investigational medicinal products; msec = milliseconds; NCI CTCAE = national cancer institute common terminology criteria for adverse events; NSCLC = non-small cell lung cancer; NR = not reported; PRO = patient reported outcome; RECIST = response evaluation criteria in solid tumors; RT-PCR = reverse transcription polymerase chain reaction.

Assessment of Heterogeneity

The sponsor assessed for clinical heterogeneity across the ITCs. Regarding the eligibility criteria, the main source of heterogeneity was related to previous treatment received, with the ALTA-1L trial including less treatment-naïve patients (approximately 73%) compared to the ALEX (100%) and ASCEND-4 (95%) trials. Related to baseline characteristics, the main difference that was noted was the imbalance in brain CNS-metastases, which was higher in ALEX (approximately 40%) compared to ALTA-1L (approximately 29%) and ASCEND-4 (approximately 32%). Another difference was the proportion of patients who switched treatments during the trials. ALEX did not permit switching between crizotinib and alectinib. In ALTA-1L, 53% of patients switched from crizotinib to brigatinib and 67.9% of crizotinib patients switched to a second-line ALK-inhibitor compared to only 22.8% of brigatinib patients who switched to a second-line ALK-inhibitor. Although treatment switching was allowed in the ASCEND-4 trial, the number of patients who switched treatments was not reported. Another difference was noted related to the median duration of follow-up, which was the longest for the ALEX trial (37.8 months), compared with 24.9 months for the ALTA-1L trial, and the shortest for the ASCEND-4 trial (19.7 months). Related to outcome assessment, ALTA-1L and ASCEND-4 assessed PFS by BIRC, yet ALEX assessed PFS as per investigator-assessment.[8]

Patient Characteristics

The patient characteristics for the three included trials are provided in Table 21. The majority of patients included in the ALEX (100%) and ASCEND-4 (95%) trials were treatment-naïve, whereas approximately 73% were treatment-naïve in the ALTA-1L trial. Less patients in the ALTA-1L trial were current smokers (brigatinib 2.9%, crizotinib 5.1%) compared to the ASCEND-4 (ceritinib 8%, chemo 8%) and ALEX (alectinib 8%, crizotinib 3%) trials. Baseline brain CNS-metastases was the highest in the ALEX trial (crizotinib 38%, alectinib 42%) compared with the ALTA-1L (brigatinib 29.2%, crizotinib 29.7%) and ASCEND-4 (ceritinib 31%, chemo 33%) trials.[8] The following baseline characteristics were considered for inclusion in the ITCs: age (continuous), sex (male versus female), ECOG PS (0-1 versus 2), brain metastases (yes versus no), smoking status (former or current versus never), receipt of any prior chemotherapy (yes versus no), and ethnicity (Asian versus non-Asian).[8]

Table 21: Patient Characteristics for the Included Trials

Trial Intervention	Population, # randomized	Mean age, Range	% female	% race	% smoking	% disease stage	% ECOG PS	% histology	% prior therapy	% baseline brain metastases
ALTA-1L										
Brigatinib	TN or 1 prior, 137	57.9, 27-86	50.4	Asian: 43.1 Black/Af/Am: 0 White: 55.5 Unknown: 1.5	Never: 61.3 Current: 2.9 Former: 35.8	IIIb: 5.8 IVb: 94.2	0: 42.3 1: 53.3 0 or 1: 95.6 2: 4.4	Confirmed adeno: 92.0	TN: 73.7 1-prior: 26.3	29.2
Crizotinib	TN or 1 prior, 138	58.6, 28-89	58.7	Asian: 35.5 Black/Af/Am: 1.4 White: 62.3 Unknown: 0.7	Never: 54.3 Current: 5.1 Former: 40.6	IIIb: 8.7 IVb: 91.3	0: 43.5 1: 52.2 0 or 1: 95.7 2: 4.3	Confirmed adeno: 99.3	TN: 73.2 1-prior 26.8	29.7
ASCEND-4										
Ceritinib	TN or 1 prior, 189	54.5, 22-81	54	Asian:40 Black/Af/Am:NR White: 55 Other: 5	Never: 57 Current: 8 Former: 35	IIIb: 5 IVb: 95	0: 37 1: 57 0 or 1: 93.1 2: 7	Confirmed adeno: 95	TN 95 1-prior: 5	31
Chemo	TN or 1 prior, 187	53.3, 22-80	61	Asian: 44 Black/Af/Am: NR White: 52 Other: 4	Never: 65 Current: 8 Former: 27	IIIb: 3 IVb: 97	0: 37 1: 56 0 or 1: 93.6 2: 6	Confirmed adeno: 98	TN: 95 1-prior: 5	33
ALEX										
Alectinib	TN, 152	56.3, 25-88	55	Asian: 45 Non-Asian: 55	Never: 61 Current: 8 Former: 32	NR	0: NR 1: NR 0 or 1: 93 2: 7	Confirmed adeno: 90	TN: 100 1-prior: 0	42
Crizotinib	TN, 151	53.8, 18-91	58	Asian: 46 Non-Asian: 54	Never: 65	NR	0: NR 1: NR	Confirmed adeno: 94	TN: 100	38

Trial Intervention	Population, # randomized	Mean age, Range	% female	% race	% smoking	% disease stage	% ECOG PS	% histology	% prior therapy	% baseline brain metastases
					Current: 3 Former: 32		0 or 1: 93 2: 7		1-prior: 0	

Source: pCODR Submission[8]
Af = African; Am =American; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent review committee assessed; IRF = independent review facility; NR = not reported; TN = treatment naïve.

The trial characteristics for the three included trials are provided in Table 22.[8] All were phase III, open label RCTs comparing brigatinib to crizotinib (ALTA-1L), ceritinib to chemotherapy (ASCEND-4), and alectinib to crizotinib (ALEX). The primary outcome across trials was PFS by BIRC in ALTA-1L and ASCEND-4 and PFS as per investigator assessment in ALEX. Secondary outcomes across the three trials included OS, ORR, DOR, TTR, patient-reported outcomes, and safety. The median duration of follow-up was 24.9 months in the ALTA-1L trial, 37.8 months in the ALEX trial, and 19.7 months in the ASCEND-4 trial.[8]

Table 22: Characteristics for the Included Trials

Trial	Phase, median duration follow-up	Intervention	Comparator	Primary outcome	Secondary outcomes eligible for the review
ALTA-1L	III, 24.9 months	Brigatinib (180mg QD [7-day lead-in at 90mg])	Crizotinib (250mg BID)	PFS by BIRC	PFS by INV; OS; Confirmed ORR; BOR; TTR by INV/ BIRC; DOR by INV/ BIRC; IC-PFS by BIRC; IC-ORR by BIRC; IC-TTR by BIRC; IC-DOR by BIRC; AEs; HRQoL
ASCEND-4	III, 19.7 months	Ceritinib (750mg QD)	Chemotherapy (pemetrexed + [cisplatin or carboplatin])	PFS by BIRC	PFS by INV; OS; ORR; DOR; DCR; TTR by BIRC; TTR by INV; IC-ORR by INV; IC-DCR by INV; IC-DOR by INV; IC-CBR by INV (added post hoc); PROs; Safety
ALEX	III, 37.8 months	Alectinib (600mg BID)	Crizotinib (250mg BID)	PFS by INV	PFS by IRC; OS; ORR; DOR; TTP in CNS; CNS-RR by IRC; DOR in CNS by IRC; Safety; HRQoL

Source: pCODR Submission[8]
AE = adverse events; BID = twice daily; BIRC = blinded independent review committee; BOR = best overall response; CNS = central nervous system; CNS-RR = central nervous system response rates; DCR = disease control rate; DOR = duration of response; EC-TTP = extracranial time to progression; HRQoL = health-related quality of life; IC-CBR = intracranial clinical benefit rate; IC-DOR = intracranial duration of response; IC-ORR = intracranial objective response rate; IC-PFS = intracranial progression-free survival; IC-TTP = intracranial time to progression; IC-TTR = intracranial time to response; INV = investigator-assessed; IRC = independent review committee assessed; IRF = independent review facility; IRR = independent radiological review; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; QD = once daily; RCT = randomized controlled trial; TTP = time to progression; TTR = time to response.

Risk of bias results

Overall, the trials had the following risk of bias results, as assessed by the sponsor: random sequence generation, allocation concealment, and selective reporting (all low risk of bias), blinding of participants and personnel (all high risk of bias), blinding of outcome assessment (low risk of bias for ALTA-1L and ASCEND-4, high risk of bias for ALEX), incomplete outcome data (low risk of bias for ALTA-1L and ASCEND-4, unclear risk of bias for ALEX).[71]

Results of ITC

ITC for Brigatinib versus Alectinib

No variables were matched for the Bucher's ITC analysis.

Seven variables were attempted for matching in the unanchored MAIC (age, sex, smoking status, Asian, CNS metastases, ECOG PS 2, and receipt of prior chemotherapy). Of these, the sponsor was able to match on the following six variables: age, sex, smoking status, Asian, CNS metastases, and ECOG PS 2. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment, as demonstrated in Table 23.

Table 23: Post-Matching Baseline Characteristics between ALTA-1L and ALEX in Unanchored MAIC (ALK inhibitor-naive)

Trial/Arm	Age in years	% Male	% Ever Smoked	% Asian	% CNS metastases	% ECOG 2
ALTA-1L Brigatinib unweighted	57.9	49.6	38.7	43.1	29.2	5.1
ALTA-1L Brigatinib weighted	56.3	44.7	39.5	45.4	42.1	6.6
ALEX Alectinib	56.3	44.7	39.5	45.4	42.1	6.6

Source: pCODR Submission[8]
CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group

For the anchored MAIC, only one variable; brain metastases (yes versus no), was adjusted for in the analysis. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment, as demonstrated in Table 24.[8]

Table 24: Post-Matching Baseline Brain CNS Metastases (%) between ALTA-1L and ALEX in Anchored MAIC (ALK inhibitor-naive)

Trial/Arm	ALEX Alectinib	ALTA-1L Brigatinib Unweighted	ALTA-1L Brigatinib Weighted
ALTA-1L Crizotinib	38.4	29.7	38.4
ALTA-1L Brigatinib	42.1	29.2	42.1

Source: pCODR Submission[8]
CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group

The results for the comparison of brigatinib versus alectinib are presented in Table 25.

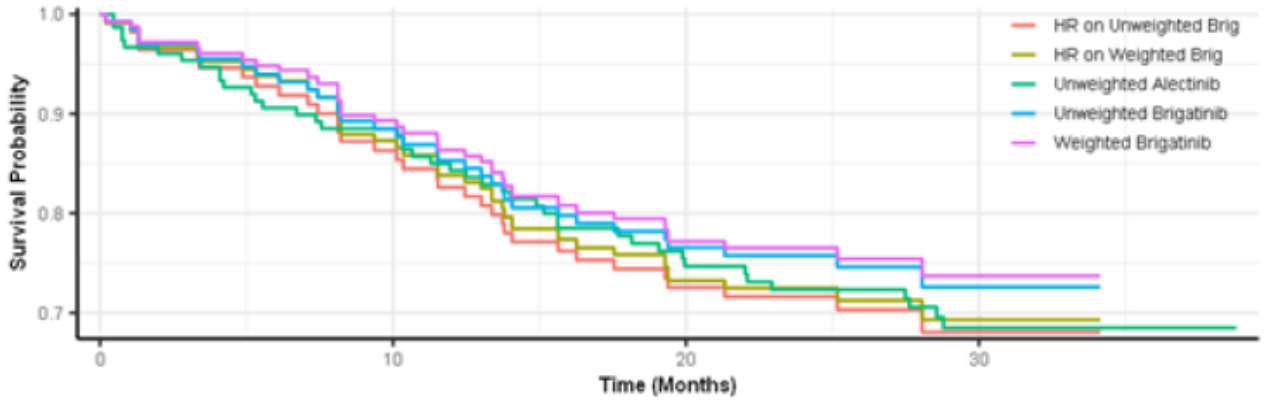
Overall survival

For OS, the estimated HRs did not favour brigatinib nor alectinib in the unweighted Bucher ITC analysis (HR 1.36, 95% CI: 0.74, 2.49), anchored MAIC (HR 1.2, 95% CI: 0.65, 2.24) or unanchored MAIC (HR 0.83, 95% CI: 0.52, 1.33). The Kaplan Meier curves for the unanchored analysis are provided in Figure 24. In addition, for the unweighted Bucher ITC and anchored MAIC a series of treatment switch-adjusted modelled analyses were conducted at different time points, as the outcomes were assessed at different times, showing similar results with a median duration of 37.8 months follow-up (Figure 25) and 27.8 months follow-up (Figure 26) for alectinib.

Figure 24: Kaplan Meier Plot for OS in Unanchored MAIC

KM plots comparing brigatinib and alectinib: Unanchored MAIC

Figure 12. Overall Survival: ITT population

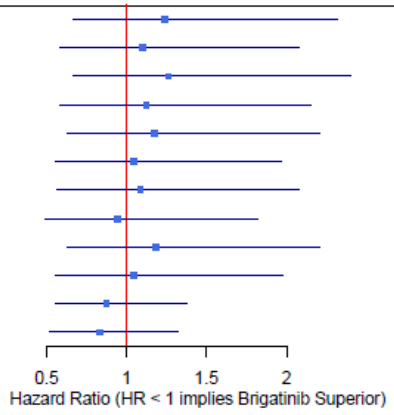


"Weighted" = MAIC re-weighted data; "Unweighted" = No weights applied to data
"HR on" = Unanchored MAIC hazard ratio (alectinib as active) applied to specified brigatinib KM curve

Source: Sponsor's response checkpoint meeting[66]

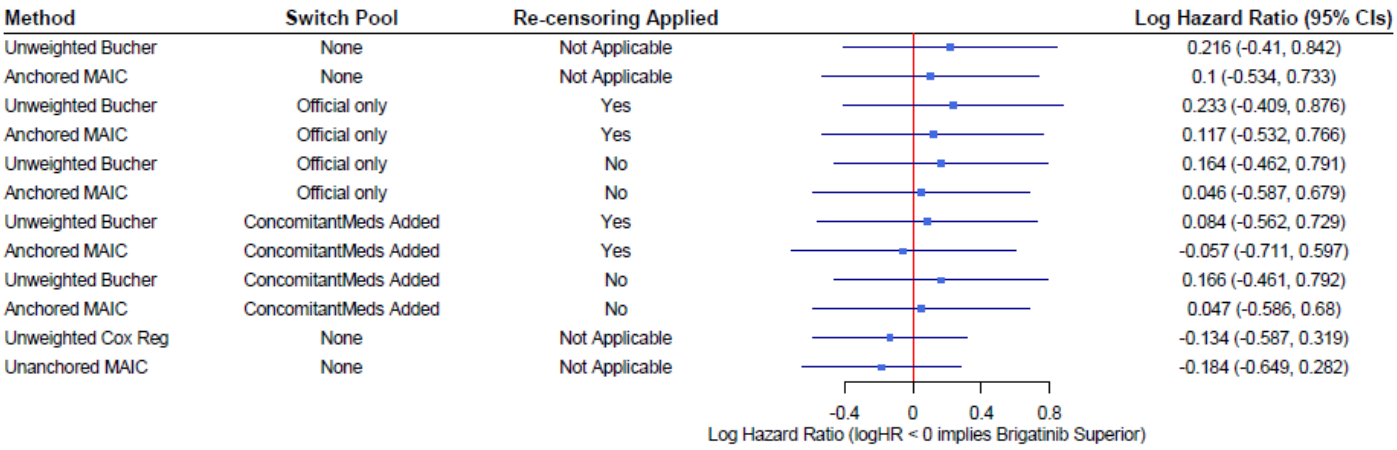
Figure 25: Summary of OS Results Based on Treatment Switch Adjustment Analyses (37.8 Months Follow-up for Alectinib) (ALK inhibitor-naive)

Method	Switch Pool	Re-censoring Applied	Hazard Ratio (95% CIs)
Unweighted Bucher	None	Not Applicable	1.241 (0.664, 2.321)
Anchored MAIC	None	Not Applicable	1.105 (0.586, 2.082)
Unweighted Bucher	Official only	Yes	1.263 (0.664, 2.402)
Anchored MAIC	Official only	Yes	1.124 (0.587, 2.15)
Unweighted Bucher	Official only	No	1.179 (0.63, 2.205)
Anchored MAIC	Official only	No	1.047 (0.556, 1.971)
Unweighted Bucher	ConcomitantMeds Added	Yes	1.087 (0.57, 2.073)
Anchored MAIC	ConcomitantMeds Added	Yes	0.945 (0.491, 1.817)
Unweighted Bucher	ConcomitantMeds Added	No	1.181 (0.631, 2.209)
Anchored MAIC	ConcomitantMeds Added	No	1.048 (0.557, 1.974)
Unweighted Cox Reg	None	Not Applicable	0.875 (0.556, 1.376)
Unanchored MAIC	None	Not Applicable	0.832 (0.522, 1.325)



Source: Sponsor Submitted MAIC[8]

Figure 26: Summary of OS Results Based on Treatment Switch Adjustment Analyses (27.8 Months Follow-up for Alectinib) (ALK inhibitor-naive)



Source: Sponsor Submitted MAIC[8]

Objective response rate
For investigator-confirmed ORR, the estimated OR did not favour brigatinib nor alectinib in the unweighted Bucher ITC analysis (OR 1.0, 95% CI: 0.49, 2.01) or anchored MAIC (OR 1.08, 95% CI: 0.53, 2.21), which was consistent with the investigator-confirmed and investigator-unconfirmed results (unweighted Bucher ORR 1.11, 95% CI: 0.51, 2.43), or anchored MAIC (ORR 1.26, 95% CI: 0.57, 2.78).

Progression-free survival

For PFS as per BICR, the estimated HR did not favour brigatinib nor alectinib in the unweighted Bucher ITC analysis HR 1.04 (95% CI: 0.65, 1.66), anchored MAIC (HR 0.97, 95% CI: 0.61, 1.55), or unanchored MAIC (HR 0.97, 95% CI: 0.69, 1.38[66]), which was consistent with the investigator confirmed PFS results.

Duration of response

For DOR, the estimated HR did not favour brigatinib nor alectinib in the unweighted Bucher ITC analysis (HR 1.11, 95% CI: 0.64, 1.91), anchored MAIC (HR 1.07, 95% CI: 0.62, 1.84) or unanchored MAIC (HR 1.06, 95% CI: 0.71, 1.65).

Table 25: Summary of results for Brigatinib versus Alectinib for ALKi-Naïve patients

Outcome	Method	Effective sample size Brigatinib	Effective sample size Alectinib	Effect size (95% CI)
OS	Unweighted Bucher ITC	137	138	HR 1.36 (0.74, 2.49)
OS	Anchored MAIC	126.8	133.2	HR 1.21 (0.65, 2.24)
OS	Unanchored MAIC	124	N/A	HR 0.83 (0.52, 1.33)
ORR (investigator confirmed + unconfirmed)	Unweighted Bucher ITC	137	138	OR 1.11 (0.51, 2.43)
ORR (investigator confirmed + unconfirmed)	Anchored MAIC	126.8	133.2	OR 1.3 (0.57, 2.78)
ORR (investigator confirmed)	Unweighted Bucher ITC	137	138	OR 1.0 (0.49, 2.01)
ORR (investigator confirmed)	Anchored MAIC	126.8	133.2	OR 1.08 (0.53, 2.21)

Outcome	Method	Effective sample size Brigatinib	Effective sample size Alectinib	Effect size (95% CI)
PFS (BIRC)	Unweighted Bucher ITC	137	138	HR 1.04 (0.65, 1.66)
PFS (BIRC)	Anchored MAIC	126.8	133.2	HR 0.97 (0.61, 1.55)
PFS (BIRC)	Unanchored MAIC	124.0	N/A	HR 0.97 (0.69, 1.38)
PFS (investigator)	Unweighted Bucher ITC	137	138	HR 1.05 (0.67, 1.64)
PFS (investigator)	Anchored MAIC	126.8	133.2	HR 0.97 (0.62, 1.52)
PFS (investigator)	Unanchored MAIC	124.0	N/A	HR 0.97 (0.68, 1.38)
DOR	Unweighted Bucher ITC	108	94	HR 1.11 (0.64, 1.91)
DOR	Anchored MAIC	104.4	90.78	HR 1.07 (0.62, 1.84)
DOR	Unanchored MAIC	100.8	N/A	HR 1.06 (0.71, 1.65)

Source: pCODR Submission[8] Abbreviations: ALKi = anaplastic lymphoma kinase inhibitor; BIRC = blinded independent review committee; CI = confidence interval; ESS = effective sample size; INV = investigator; MAIC = matching-adjusted indirect comparison.

DOR = duration of response; HR = hazard ratio; ITC = indirect treatment comparison; N/A = not applicable; OS = overall survival; OR = odds ratio; ORR = objective response rate; PFS = progression free survival;

MAIC for Brigatinib versus Ceritinib

Seven variables were attempted for matching in the MAIC for brigatinib versus ceritinib (age, sex, smoking status, Asian, CNS metastases, ECOG PS 2, and receipt of any prior chemotherapy) and the sponsor was able to match on all seven variables. A comparison of baseline patient characteristics post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables after adjustment, as demonstrated in Table 26.[8]

Table 26: Post-Matching Baseline Characteristics between ALTA-1L and ASCEND-4 in Unanchored MAIC

Trial/Arm	Age in years	% Male	% Ever Smoked	% Asian	% CNS metastases	% ECOG 2	Prior chemo
ALTA-1L Brigatinib unweighted	57.9	49.6	38.7	43.1	29.2	5.1	26.3
ALTA-1L Brigatinib weighted	54.5	46.0	42.9	40.2	31.2	6.9	5.3
ASCEND-4 Ceritinib	54.5	46.0	42.9	40.2	31.2	6.9	5.3

Source: pCODR Submission[8]

Overall survival, objective response rate, and progression-free survival

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group

The results for the unanchored MAIC comparisons of brigatinib versus ceritinib are presented in Table 27. For OS, the estimated HR did not favour brigatinib nor ceritinib (HR 0.69, 95% CI: 0.41, 1.15). These results were consistent for investigator-unconfirmed ORR (OR 1.64, 95% CI: 0.91, 2.96) and PFS as per BIRC (HR 0.73, 95% CI: 0.51, 1.04). However, the results for PFS as per investigator assessment were statistically significant in favour of brigatinib (HR 0.61, 95% CI: 0.42, 0.90).

Table 27: Summary of Unanchored MAIC results for Brigatinib versus Ceritinib for ALKi-Naïve patients

Outcome	Effective sample size Brigatinib	Effect size (95% CI)
OS	93.8	HR 0.69 (0.41, 1.15)
ORR (investigator unconfirmed)	93.8	OR 1.64 (0.91, 2.96)
PFS (BIRC)	93.8	HR 0.73 (0.51, 1.04)
PFS (investigator)	93.8	HR 0.61 (0.42, 0.90)

Source: pCODR Submission[8] Abbreviations: ALKi = anaplastic lymphoma kinase inhibitor; BIRC = blinded independent review committee; CI = confidence interval; ESS = effective sample size; INV = investigator; MAIC = matching-adjusted indirect comparison.

HR = hazard ratio; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression free survival

Critical Appraisal

The quality of the sponsor-submitted MAIC was appraised according to best practice principles outlined by Phillippo et al. (2018).[11] The pCODR Methods Team noted the following:

- *Systematic review conduct:* The systematic review methods were conducted with some limitations including that the sponsor selected specific studies for inclusion in the MAIC without reporting a rationale for all selections. An example is excluding the trials that only included Japanese patients. This may have led to relevant data being excluded in the MAICs.

- *Heterogeneity:* The differences in inclusion/exclusion criteria across the studies introduced heterogeneity, as the index trial with IPD (ALTA-1L) had broad inclusion criteria, which included patients who were treatment-naïve or not. In comparison, ASCEND-4 and ALEX included patients who were treatment-naïve. Given that there was no prior matching procedure before weighting to select patients who match on number of prior treatments from the IPD, this heterogeneity was not accounted for in the MAICs for the comparison of brigatinib versus alectinib. There was a greater proportion of patients with CNS metastases at baseline in the ALEX trial, however, this was a variable that was adjusted for in the MAICs in the comparison versus alectinib and versus ceritinib. Substantial cross-over occurred in the ALTA-1L trial, yet this was not permitted in the ALEX trial and although it was allowed in the ASCEND-4 trial, the results were not reported. This could bias the OS results and although a series of treatment switching analyses were conducted to adjust for this, the results should be interpreted with caution as they may not reflect a reliable adjustment for treatment switching, given inherent limitations with the method used and the immature OS data for brigatinib. Furthermore, the ALEX trial included a higher proportion of patients with baseline brain CNS metastases than the ALTA-1L and ASCEND-4 trials, which may reflect a patient population with more advanced disease compared with other trials. However, this was adjusted for in the MAICs. The primary outcome across trials was PFS by BIRC in ALTA-1L and ASCEND-4 and PFS as per investigator assessment in ALEX, this again is a difference that can not be accounted for in MAIC. Differing lengths of follow-up (ranging from 19.7 to 37.8 months) between the trials can also contribute to heterogeneity, especially for survival analysis, and although separate analyses were conducted at different time points for the brigatinib versus alectinib Bucher ITCs, this was not adjusted for in the MAICs versus alectinib or ceritinib.

- *Selection of variables for matching:* The analyses included a mixture of Bucher ITCs, anchored MAICs, and unanchored MAICs. For the anchored MAICs, all effect modifiers need to be adjusted for and for unanchored MAICs, both effect modifiers and prognostic variables need to be adjusted for in the analysis. It is unlikely that all effect modifiers and prognostic variables can be adjusted for in MAICs; only seven variables were attempted and there are likely many more that are relevant to this topic. Furthermore, MAICs can not account for unknown cross-trial differences; thus, the MAIC estimates are susceptible to bias from unknown confounding. Several variables (e.g., differences in outcome assessment, differences in duration of follow-up) can not be adjusted for in MAICs making interpretation of results difficult. Furthermore, it is a requirement in MAICs to assess the degree of residual bias in MAIC estimates. This was not provided in the sponsor's report. The CGP panel agreed that the proportion of patients with brain CNS metastases at baseline (as these patients have worse outcomes overall) and proportion of treatment naïve patients at baseline could potentially affect the treatment effect. The latter variable was not adjusted for the brigatinib versus alectinib comparison. Furthermore, the OS data were immature, and the number of deaths observed in the ALTA-1L trial may have been insufficient to adequately adjust for treatment switching, given the immaturity of the OS data. Accordingly, the magnitude of the bias in the estimates of the treatment effects remains unknown.

- *Effective sample size:* A comparison of baseline characteristics between the trials pre- and post-matching was provided, which indicated successful matching was obtained for the analysis. For ALTA-1L, the effective sample size for the brigatinib group was reduced by 25% when compared to alectinib in the ALEX trial and 32% compared to ceritinib in the ASCEND-4 trial, which is considered reasonable for a MAIC. For the ALEX trial, the effective sample size for the alectinib group was reduced by 40% when compared to brigatinib, which is also considered reasonable for MAIC. However, for the anchored MAIC, only one variable was adjusted for based on their effect modifier analysis from the ALTA-1L trial, and this trial may not have had sufficient power to adequately identify all effect modifiers, which is a limitation.
- *Analysis:* Some of the methods used for the Bucher ITC analysis and MAIC were not appropriate, such as selection of one group in a multi-arm trial, which is not recommended. In addition, there was not an analysis for the residual bias for MAIC estimates. Based on all of these limitations, no comparisons can be made across these ITCs.

7.1.3 Summary

The sponsor conducted several ITC analyses to provide comparative efficacy estimates between brigatinib and alectinib, as well as brigatinib and ceritinib for first-line treatment of adult patients with ALK+ NSCLC. The ITCs performed included Bucher ITC, unanchored MAICs, and anchored MAICs to derive comparative estimates for the outcomes of OS, ORR, PFS, and DOR. The methods and results of the ITCs were critically appraised by the pCODR Methods Team according to best practice principles for MAICs.[11] The results did not favour brigatinib over alectinib or brigatinib over ceritinib for any of the outcomes, except for PFS as per investigator assessment in the comparison of brigatinib versus ceritinib, which demonstrated statistically significant results in favour of brigatinib over ceritinib. The pCODR Methods Team concluded all ITC results should be interpreted with consideration of the several limitations associated with the analyses, such as heterogeneity between studies, inability to adjust for all potential confounders and prognostic variables and use of inappropriate analysis methods for MAIC (e.g., not providing residual bias estimates for MAICs). The ITCs were performed by a consultancy group hired by the sponsor. As a result, the information provided in the reports should be viewed considering this potential conflict of interest. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with brigatinib.

7.2 Critical Appraisal of the Elliott et al.[12] Published Indirect Treatment Comparison Using Network Meta-Analysis

7.2.1 Objective

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. A recently published NMA[12] was identified through the literature search conducted by the CADTH team that was relevant to the sponsor's submission. The focus of the NMA was to examine the relative effects of ALK-inhibitors among patients with ALK- or ROS1-positive NSCLC.

7.2.2 Findings

A published NMA that was relevant to the sponsor's submission is described and critically appraised in the sections below.

Methods

Systematic review

The published systematic review was based on searches of MEDLINE, Embase, and the Cochrane Library in July 2019 without any date or language limitations imposed. In addition, clinical trial registries, and regulatory agency websites were searched. The eligibility criteria for the systematic review were RCTs including treatment-naïve or experienced patients with stage III or IV ALK-

positive or ROS-positive NSCLC, any type of ALK-inhibitor compared with each other or placebo, chemotherapy, or radiotherapy, reporting on the following outcomes: treatment-related death (primary), OS, PFS, and SAEs (Table 28).

Table 28: PICOS Eligibility Criteria

PICOS Item	Eligibility Criteria
Population	Treatment-naïve or experienced participants with stage III or IV ALK-positive and/or ROS1-positive NSCLC
Interventions	ALK inhibitors (e.g, crizotinib, ceritinib, alectinib, brigatinib, loratinib, ensartinib, and entrectinib).
Comparators	Placebo, chemotherapy, radiotherapy, another ALK inhibitor, or the same ALK inhibitor at a different dose
Outcomes	Efficacy outcomes: • Progression-free survival • Overall survival Harms outcomes: • Treatment-related death (primary) • Serious adverse events
Study design	Randomized controlled trials

Source: Elliott et al.[12] Abbreviations: ALK+ = anaplastic lymphoma kinase positive; NSCLC = non-small cell lunch cancer.

; PICOS =population, intervention, comparator, outcome, study type

Regarding the conduct of the systematic review, the protocol was registered in the PROSPERO database, literature search was peer-reviewed using the PRESS checklist, literature search results were screened by two reviewers independently, data were abstracted by one reviewer and verified by another, and risk of bias was appraised by two reviewers independently using the Cochrane risk of bias tool. All disagreements were resolved through discussion.

Methods for indirect treatment comparisons

Pairwise meta-analyses were conducted as well as NMAs for all outcomes were performed in a Bayesian environment using the WinBUGs software with chemotherapy as the reference group. For meta-analyses and NMA, clinical heterogeneity was examined by comparing the patient characteristics across the trials. For meta-analyses and NMA, statistical heterogeneity was assessed using the I^2 statistic, with anything >75% considered substantial heterogeneity precluding analysis. Sub-group analysis was conducted based on previous treatment (naïve versus experienced). Model fit (fixed versus random effects) was assessed using the deviance information criterion. The fixed effect model was selected, based on similarity of the trials and model fit diagnostics. For meta-analyses and NMA, for the time-to-event outcomes, a normal likelihood with identity link model was used, whereas a binomial likelihood model logit link was used for dichotomous outcomes. Point estimates (OR, relative risk or RR, risk difference or RD, HR) and 95% credible intervals (CrIs) were estimated using the Markov Chain Monte Carlo methods. Vague priors were used for the basic parameters (N (0, 100^2)), whereas informative priors were used for between-study variance. Model convergence was assessed using trace plots and Brooks-Gelman-Rubin statistics. Inconsistency was assessed by comparing the posterior mean deviance of individual data points in the inconsistency model with those from the consistency model. It was deemed that the consistency model was a better fit for the data than the inconsistency model. The transitivity assumption was assessed by comparing study and patient characteristics. Publication bias was not assessed, due to the small number of trials included in each outcome.

The treatment nodes considered for the NMA included chemotherapy, ceritinib 750 QD, alectinib 300 twice daily (BID), alectinib 600 BID, crizotinib 250 BID, and brigatinib 180 once daily (QD).

Results

Systematic review results and NMA feasibility assessment

After screening 3287 citations and 1081 full-text articles, 13 RCTs met the inclusion criteria and were included in the systematic review. All three trials included in the sponsor's ITC submission were included in the systematic review (ALTA-1L[9], ALEX[4], ASCEND-4[25]).

Trial characteristics

The trial characteristics can be found in Table 29. All RCTs were open-label and most were two-arm parallel designs, except for one that was a cross-over trial. In six RCTs, patients could crossover to the alternative treatment after disease progression. The outcomes assessed across the RCTs are provided in Table 29. Most RCTs that reported PFS employed an independent review committee to ascertain disease progression, yet three RCTs used unblinded assessment as per the trial investigators.

Table 29: Trial characteristics

Table 1. Study characteristics of included randomized controlled trials.

Author, yr, page (study name; NCT no.) (companion publications)	Population	Groups (no. randomized)	Duration of treatment, median (IQR), months	Cross-over between treatment groups allowed?	Reported outcomes of interest to this review	Funding source
Chemotherapy-controlled						
Wu 2018, p. 1549 (PROFILE 1029; NCT01639001)[28, 30]	18–70 years, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (104) Chemotherapy (103)	NR	Not reported	TR death; OS; PFS (independent review)*;	Pharma
Shaw 2013, p. 2385 (PROFILE 1007; NCT00932893) [16, 31] (Blackhall 2014[32])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with progressive disease after one prior platinum-based chemotherapy regimen	Crizotinib, 250 mg BID (173) Chemotherapy (174)	NR	Not during study period; participants from the chemotherapy arm could enroll in NCT00932451	TR death; OS; PFS (independent radiologic review*)	Pharma
Solomon 2014, p. 2167[25] (PROFILE 1014; NCT01154140) (Thorne-Nuzzo 2017, [33] Solomon 2016[34], Solomon 2018 [35])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (172) Chemotherapy (171)	10.9 (range 0.4 to 34.3) 4.1 (range 0.7 to 6.2)	Yes; participants in the chemotherapy arm with disease progression could cross to the crizotinib arm provided safety criteria were met	TR death; OS; PFS (independent review)*	Pharma
Zhao 2015, p. 616[18]	≥ 18 yr, ALK-positive NSCLC, Karnofsky performance status (KPS) score ≥ 70, following first- or second-line chemotherapy	Crizotinib, 250 mg BID (14) Chemotherapy (14)	NR	Not reported	TR death; SAEs	Non-pharma
Novello 2018, p. 1409 (ALUR; NCT02604342) [26]	ALK-positive NSCLC, with ECOG score of 0–2; two prior lines of systemic therapy including one line of chemotherapy and one of crizotinib	Alectinib 600 mg BID (72) Chemotherapy (35)	20.1 wk (range 0.4–62.1) 6.0 wk (range 1.9–47.1)	Yes; cross-over from chemotherapy to alectinib was permitted following progression	OS; PFS (investigator-assessed)*	Pharma
Soria 2017, p. 917 [24, 36] (ASCEND-4; NCT01828099)	≥ 18 yr, ALK-positive NSCLC, ECOG score of 0–2, previously untreated	Ceritinib 750 mg QD (189) Chemotherapy (187)	66.4 (30.8 to 83.7) 29.9 (13.0 to 62.3)	Yes, participants in the chemotherapy arm could crossover to ceritinib after disease progression	TR death; OS; PFS (independent review)*; SAEs	Pharma
Shaw 2017, p. 874 (ASCEND-5, NCT01828112) [23, 37] (Kiura 2018 [38])	≥ 18 yr, ALK-positive NSCLC, with WHO performance status of 0–2, one or two previous chemotherapy regimens and previous crizotinib for at least 21 d	Ceritinib 750 mg QD (115) Chemotherapy (116)	30.3 (13.3 to 54.1) 6.3 (6.0 to 15.1)	Yes, participants in the chemotherapy arm could cross over to the ceritinib group after disease progression	TR death; OS; PFS (independent review)*	Pharma
Head-to-head comparisons of ALK inhibitors						
Zhou 2019, p. 437 (ALESIA; NCT02838420) [29]	≥ 18 yr, ALK-positive NSCLC, ECOG score of 0–2, life expectancy of >12 wk, no prior systemic therapy	Crizotinib 250 mg BID (62) Alectinib 600 mg BID (125)	12.6 14.7	No	TR death; OS; PFS (investigator assessed)*; SAEs	Pharma
Camidge 2018, p. 1 (ALTA-1L; NCT02737501)[25]	≥ 18 yr, ALK-positive locally advanced or metastatic NSCLC, with at least one measurable lesion, and no prior ALK-targeted therapy	Crizotinib 250 mg BID (138) Brigatinib 180 mg QD (137)	7.4 (range 0.1 to 19.2) 9.2 (range 0.1 to 18.4)	Yes; patients in the crizotinib group could cross over to brigatinib after disease progression	TR death; OS; PFS (independent review)*	Pharma
Peters 2017, p. 829 (ALEX; NCT02075840) [5, 39] (Camidge 2019 [40]; Gadgeel 2018[41])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (151) Alectinib 600 mg BID (152)	17.6 (0.3 to 27.0) 18.6 (0.5 to 29.0)	No	TR death; OS; PFS (investigator assessed)*	Pharma

Table 1. (Continued)

Author, yr, page (study name; NCT no.) (companion publications)	Population	Groups (no. randomized)	Duration of treatment, median (IQR), months	Cross-over between treatment groups allowed?	Reported outcomes of interest to this review	Funding source
Hida 2017, p. 29 [21] (J-ALEX; JAPICcti-132316)	≥ 20 yr, ALK-positive NSCLC, with ECOG score of 0–2, ALK-inhibitor naive, chemotherapy-naïve or had received 1 regimen of chemotherapy	Crizotinib 250 mg BID (104) Alectinib 300 mg BID (103)	NR	Not during study period; Treatment crossover after study withdrawal was allowed in both groups	TR death; PFS (independent review)*	Pharma
Hida 2016, p. 1642 (JP28927; JapicCTI-132186) [19] (Nishio 2018 [42])	≥ 20 yr, ALK-positive NSCLC, with ECOG score of 0–1; prior treatment, including other ALK inhibitors, was allowed	Cross-over (300 mg BID total for all groups; 35 participants): Alectinib 20/40 mg capsules Alectinib 150 mg capsules Extension: Alectanib 300 mg BID (150 mg capsules)	13.1 (range 11.1 to 15.0)	Yes by design during cross-over phase	TR death	Pharma
Kim 2017 (ALTA, NCT02094573) [22, 43] (Kawata 2019 [44])	≥ 18 yr, ALK-positive NSCLC, with ECOG performance status of 0–2, disease progression while receiving crizotinib	Brigatinib 90 mg QD (109) Brigatinib 180 mg QD (110)	NR	Yes, participants in the 90 mg/d group could cross to the 180 mg/d group after disease progression	PFS (independent review), SAEs	Pharma

BID = twice daily, ECOG = Eastern Cooperative Oncology Group, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, QD = once daily, RCT = randomized controlled trial, SAE = serious adverse event, TR = treatment-related, WHO = World Health Organization.

*Primary outcome.

https://doi.org/10.1371/journal.pone.0229179.t001

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

All RCTs included ALK-positive patients; no ROS-1 patients were included in the RCTs. Seven RCTs compared an ALK-inhibitor to chemotherapy and six RCTs compared ALK-inhibitors with each other. The ALK-inhibitors examined were crizotinib, alectinib, ceritinib, and brigatinib. Additional patient characteristics can be found in Table 30.

Table 30: Patient characteristics in the included trials

Table 2. Participants characteristics of included randomized controlled trials.

Author, yr, page (study name; NCT no.)	Group	Age, yr, median (range)*	Male, %	Current smoking,%	Never smoked,%	Brain or CNS metastases, %	ECOG0, %	ECOG 1, %	ECOG2, %	Adenocarcinoma, %
Treatment naive										
Zhou 2019[29] (ALESIA; NCT02838420)	Crizotinib	49 (IQR 41 – 59)	55	5	73	37	98**		2	97
	Alectinib	51 (IQR 43 – 59)	51	3	67	35	97**		3	94
Wu 2018[28] (PROFILE 1029; NCT01639001)	Chemotherapy	50 (23–69)	42	9	70	31	96**		4	98
	Crizotinib	48 (24–67)	48	7	75	20	96**		4	96
Camidge 2018[25] (ALTA-1L; NCT02737501)	Crizotinib	60 (29–89)	41	5	54	30	96**		4	99
	Brigatinib	58 (27–86)	50	3	61	29	96**		4	92
Soria 2017, p. 917 (ASCEND-4; NCT01828099)	Chemotherapy	54.0 (22–80)	39	8	65	33	37†	56†	6†	98
	Ceritinib	55.0 (22–81)	46	8	57	31	37	57	7	95
Peters 2017[5] (ALEX; NCT02075840)	Crizotinib	54.0 (18–91)	42	3	65	38	93**		7	94
	Alectinib	58.0 (25–88)	45	8	61	42	93**		7	90
Solomon 2014[17] (PROFILE 1014; NCT01154140)	Chemotherapy	54 (19–78)	37	3	65	27	95**		5	94
	Crizotinib	52 (22–76)	40	6	62	26	94**		6	94
Treatment experienced										
Novello 2018[26] (ALUR; NCT02604342)	Chemotherapy	59 (37–80)	49	6	46	74	31	54	14	100
	Alectinib	55.5 (21, 82)	57	3	49	65	40	51	8	100
Hida 2017[21] (J-ALEX; JAPICcti-132316)	Crizotinib	59.5 (25–84)	39	3	59	28	46	52	2	99
	Alectinib	61.0 (27–85)	40	2	54	14	52	46	2	97
Kim 2017[22] (ALTA; NCT02094573)	BRI 90 QD	50.5 (18–82)	45	NR	63	71	30	63	6	96
	BRI 180 QD	56.5 (20–81)	42	NR	57	67	41	51	8	98
Shaw 2017[23] (ASCEND-5; NCT01828112)	Chemotherapy	54.0 (47.0–64.0)¶	47	1	53	59	44†	52†	4†	97
	Ceritinib	54.0 (44.0–63.0)¶	41	3	62	57	49	43	8	97
Hida 2016[19] (JP28927; JapicCTI-132186)	Alectinib (cross-over)	45.0 (21–78)	46	3	60	NR	43	57	NR	100
Zhao 2015[18]	Chemotherapy	58.1 (13.2)‡	64	NR	NR	NR	NR	NR	NR	29
	Crizotinib	55.3 (12.7)‡	57	NR	NR	NR	NR	NR	NR	43
Shaw 2013[16] (PROFILE 1007; NCT00932893)	Chemotherapy	49 (24–85)	45	5	64	34	37	55	8	94
	Crizotinib	51 (22–81)	43	3	62	35	42	49	9	95

BRI = brigatinib, CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, IQR = interquartile range, NR = not reported, QD = once daily, SD = standard deviation.

*Unless otherwise stated.

†WHO performance score.

‡Mean (SD).

¶Median (IQR).

** ECOG0 or ECOG1.

https://doi.org/10.1371/journal.pone.0229179.t002

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from:

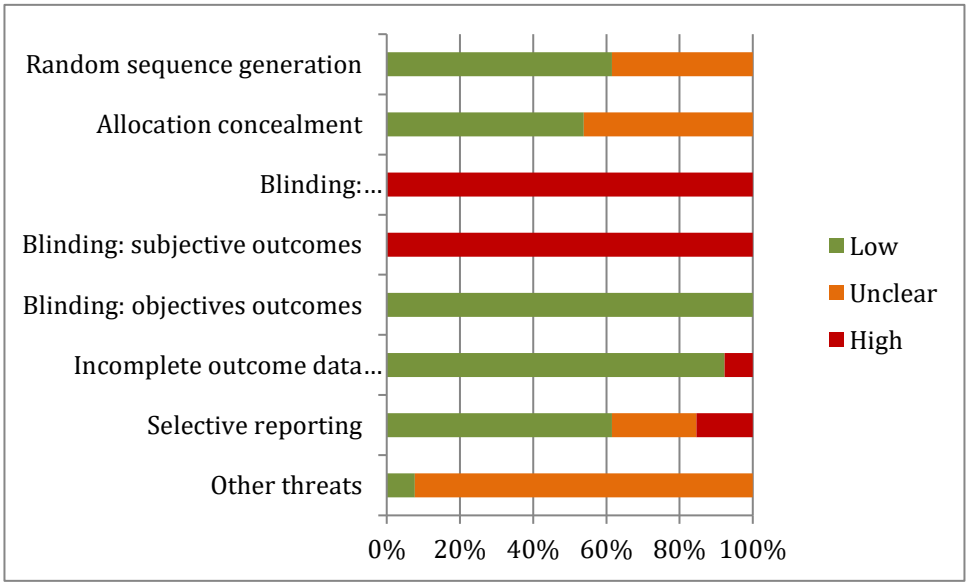
Assessment of Homogeneity

The authors assessed heterogeneity prior to conducting the NMA. It was deemed that overall, the mean age, sex, ECOG status, and history of smoking variables were well-balanced across the trials. The only exception was the adenocarcinoma variable, which differed for an RCT[72] that enrolled a larger percentage of patients with squamous NSCLC compared to the others. The heterogeneity was also assessed statistically. For the consistency assumption, the consistency model was a better fit for the data than the inconsistency model, suggesting that the consistency assumption was satisfied.

Risk of Bias Assessment

The risk of bias results can be found in Figure 27. The authors noted that randomization and allocation concealment was deemed a low risk of bias overall. However, performance and detection bias were of concern due to the open label nature of the included RCTs. Furthermore, two RCTs were at a high risk of bias related to selective reporting due to differences between the protocol and final RCT report. Other concerns that were noted by the authors included cross-over between study groups, with unclear reporting of outcome data by group allocation.

Figure 27: Risk of bias results



Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Results of NMA

A summary of the results for all outcomes is presented in Table 31.

Treatment-related deaths

NMA was not possible for treatment-related deaths. A pairwise meta-analysis was conducted including six RCTs and the results are presented in Table 32. The estimated OR did not favour ALK-inhibitors nor chemotherapy (OR 2.59, 95% CrI: 0.76, 11.37). Similar results were observed in a sub-group analysis conducted for patients who were treatment-naïve (OR 2.59, 95% CrI: 0.76, 11.37) or treatment-experienced (OR 2.23, 95% CrI: 0.40, 19.66).

Overall survival

For OS, nine RCTs were included in the NMA (Figure 28) and the results are presented in Tables 33 and 34. Based on the HRs, chemotherapy was inferior to alectinib (HR 0.57, 95% CrI: 0.39, 0.83) and crizotinib was also inferior to alectinib (HR 0.68, 95% CrI: 0.48, 0.96) with no other differences observed between the other ALK-inhibitors, including for brigatinib versus alectinib (HR 1.44, 95% CrI: 0.68, 3.08) or all of the comparators. A sub-group analysis was conducted restricted to treatment-naïve patients and the same results were observed (brigatinib versus alectinib: HR 1.55, 95% CrI: 0.72, 3.34). A second sub-group analysis was conducted restricted to treatment-experienced patients, yet brigatinib was not a treatment node in this NMA and as such, no results were provided for alectinib versus brigatinib.

Progression-free survival

For PFS, 10 RCTs were included in NMA (Figure 29) and the results are presented in Tables 35 and 36. All ALK-inhibitors were favoured over placebo based on the HRs (crizotinib: HR 0.46, 95% CrI: 0.39, 0.54; ceritinib: HR 0.52, 95% CrI: 0.42, 0.64; alectinib 300 BID: 0.16, 95% CrI: 0.08, 0.33; alectinib 600 mg BID: 0.23, 95% CrI: 0.17, 0.30; brigatinib: HR 0.23, 95% CrI: 0.15, 0.35). Comparing between the ALK-inhibitors, both alectinib and brigatinib were favoured compared to crizotinib (alectinib 300 BID: HR 0.34, 95% CrI: 0.17, 0.70; alectinib 600 BID: HR 0.49, 95% CrI: 0.38, 0.63; brigatinib: HR 0.49, 95% CrI 0.33, 0.73) and ceritinib (alectinib 300 BID: HR 0.30, 95% CrI: 0.14, 0.64; alectinib 600 BID: HR 0.43, 95% CrI: 0.31, 0.62; brigatinib: HR 0.43, 95% CrI: 0.27, 0.70). No differences were observed between brigatinib 180 QD and alectinib 300 BID (HR 1.44, 95% CrI: 0.63, 3.25) and versus alectinib 600 BID (HR 1.00, 95% CrI: 0.62, 1.61). A sub-group analysis was conducted restricted to treatment-naïve patients and the same results were observed (brigatinib versus alectinib: HR 1.07, 95% CrI: 0.66, 1.75).

Serious adverse events

For SAEs, eight RCTs were included in the NMA (Figure 30) and the results are presented in Tables 37 and 38. Based on the ORs, ceritinib was favoured over crizotinib (OR 0.60, 95% CrI: 0.39, 0.93) and chemotherapy was favoured over crizotinib and alectinib (crizotinib: OR 2.08, 95% CrI: 1.56–2.79; alectinib: OR 1.60, 95% CrI: 1.00, 2.58). Since brigatinib was not a treatment node in this NMA, there are no results for alectinib versus brigatinib. A second sub-group analysis was conducted restricted to treatment-experienced patients, yet brigatinib was not a treatment node in this NMA and as such, no results were provided for alectinib versus brigatinib.

Table 31: Summary of meta-analyses and NMA results

Table 3. Summary of analyses.

Outcome	Meta-analysis (class effect v. chemotherapy)				Network-meta-analysis (effect of individual ALK inhibitors)			
	No. of RCTs*	No. of participants	Effect estimate (95%CI); I^2	Finding	No. of RCTs	No. of participants	No. of comparisons	Finding
Treatment-related death	6†	1508	OR 2.58 (0.76 to 11.37), RD 0.49 (−0.16 to 1.46); 0%	• No difference in risk between crizotinib and chemotherapy; no treatment-related deaths reported for other ALK inhibitors	—	—	—	—
Overall survival	6	1611	HR 0.84 (0.72 to 0.97); 0%	• ALK inhibitors improved OS relative to chemotherapy	9	2376	9	• Alectinib improved overall survival relative to chemotherapy and crizotinib; no statistically significant difference between chemotherapy and crizotinib, ceritinib, or brigatinib
Progression-free survival	6	1611	HR 0.47 (0.41 to 0.53); 0%	• ALK inhibitors improved PFS relative to chemotherapy	10	2583	10	• Crizotinib, ceritinib, alectinib, and brigatinib were significantly better than chemotherapy • Alectinib and brigatinib were significantly better than crizotinib and ceritinib
Serious adverse events	6	1584	OR 1.67 (1.34 to 2.08); 62%	• ALK inhibitors increased the risk of SAE relative to chemotherapy	8	2074	8	• Risk of SAEs was significantly higher with crizotinib and alectinib compared with chemotherapy • Risk of SAEs was lower with ceritinib than with crizotinib

HR = hazard ratio, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trial, RD = risk difference, SAE = serious adverse event

*RCTs that involved an ALK inhibitor compared to chemotherapy.

†Six chemotherapy-controlled RCTs reported 6 treatment-related deaths among patients who received crizotinib. An additional 4 treatment-related deaths were reported among those exposed to crizotinib in head-to-head RCTs of different ALK inhibitors. See S1 File for full details.

https://doi.org/10.1371/journal.pone.0229179.t003

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 32: Treatment-related deaths: Relative risks and odds ratios (Bayesian meta-analysis)

TR deaths	Relative risk (95% Credible Interval)	Odds ratio (95% Credible Interval)
All participants	2.57 (0.76, 11.25)	2.59 (0.76, 11.37)
Experienced	2.22 (0.40, 19.24)	2.23 (0.39, 19.66)
Naïve	2.57 (0.76, 11.25)	2.59 (0.76, 11.37)

Figure 28: Network of trials for OS

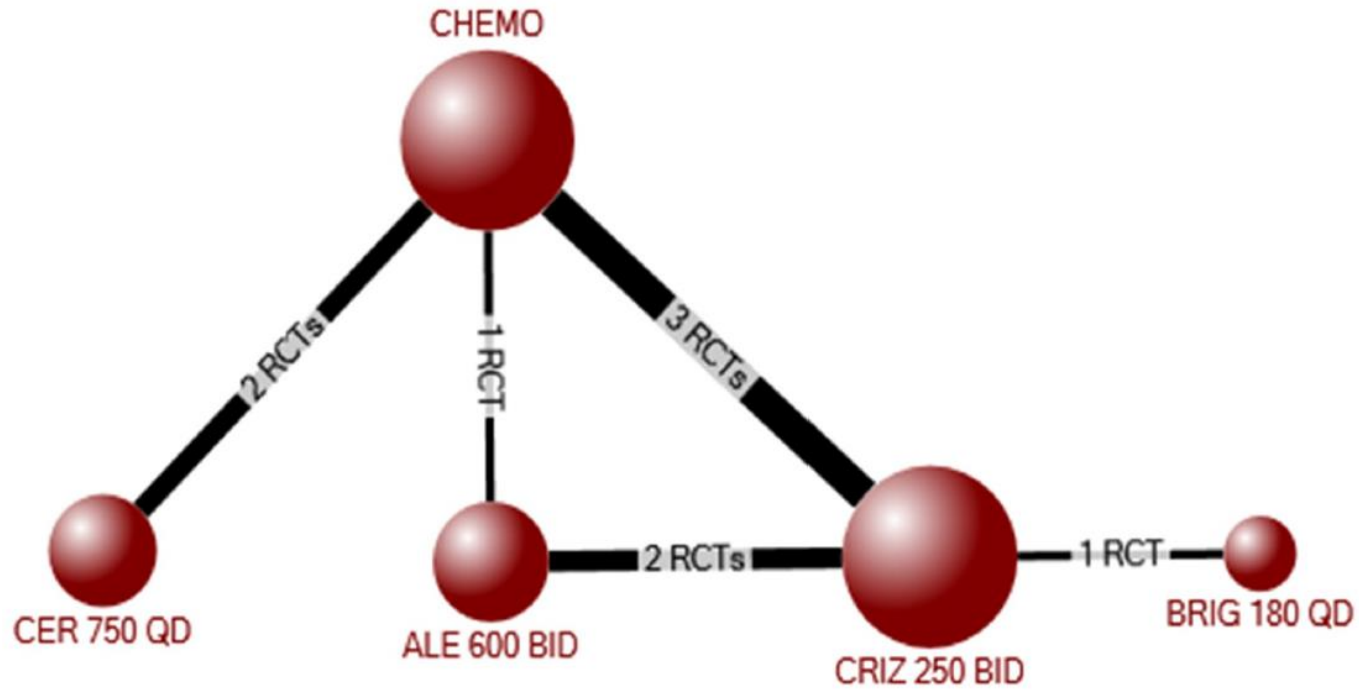


Fig 2. Evidence network for the network meta-analysis of overall survival among all participants (treatment experienced and naïve).

https://doi.org/10.1371/journal.pone.0229179.g002

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 33: Meta-analysis of all participants: Overall survival

Comparison	No. of studies	I^2 (%)	Hazard ratio (95%CrI)*
CRIZ 250 BID v. CHEMO	3	0	0.83 (0.69, 1.00)
CERT 750 QD v. CHEMO	2	27	0.85 (0.64, 1.13)
CRIZ 250 BID v. ALECT 600 BID	2	76	0.63 (0.43, 0.91)
ALECT 600 BID v. CHEMO	1	NA	0.89 (0.35, 2.25)
CRIZ 250 BID v. BRIG 180 QD	1	NA	0.98 (0.50, 1.93)

ALE = alectinib, BID = twice daily, CER = ceritinib, CHEMO = chemotherapy, CrI = credible interval, CRIZ = crizotinib, NA = not applicable, QD = once daily.
*Fixed-effects model

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 34: NMA results for all participants: Overall survival

Table 4. Network meta-analysis of hazard ratios for overall survival for individual ALK inhibitors among all patients (experienced and naïve) with ALK-positive non-small cell lung cancer.

	Hazard ratio (95% credible interval)*			
	CHEMO	CRIZ 250 BID	CER 750 QD	ALE 600 BID
CRIZ 250 BID	0.84 (0.70, 1.01)	—		
CER 750 QD	0.85 (0.64, 1.13)	1.01 (0.73, 1.41)	—	
ALE 600 BID	**0.57 (0.39, 0.83)**	**0.68 (0.48, 0.96)**	0.67 (0.42, 1.07)	—
BRIG 180 QD	0.82 (0.41, 1.65)	0.98 (0.50, 1.91)	0.97 (0.46, 2.02)	1.44 (0.68, 3.08)

ALE = alectinib, BID = twice daily, BRIG = brigatinib, CER = ceritinib, CHEMO = chemotherapy, CRIZ = crizotinib, QD = once daily.

*Fixed-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment). White indicates no significant difference between treatments.

https://doi.org/10.1371/journal.pone.0229179.t004

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Figure 29: Network of trials for PFS

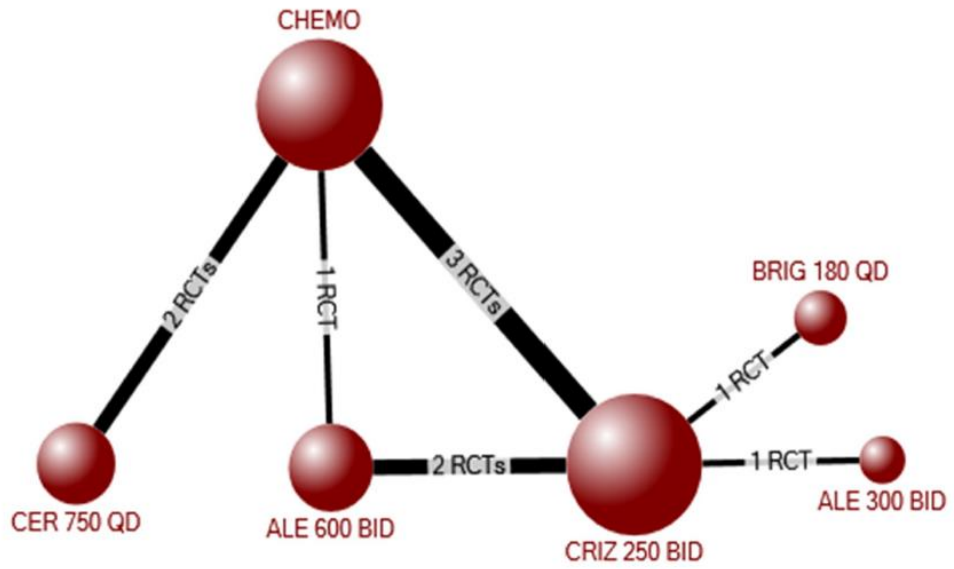


Fig 3. Evidence network for the network meta-analysis of progression-free survival among all participants (treatment experienced and naïve).

https://doi.org/10.1371/journal.pone.0229179.g003

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 35: Meta-analysis of all participants: PFS

Comparison	No. of studies	I^2 (%)	Hazard ratio (95%CrI)*
CRIZ v. CHEMO	3	0	0.45 (0.38, 0.53)
CERT v. CHEMO	2	0	0.52 (0.42, 0.64)
CRIZ v. ALECT (600 BID)	2	0	0.46 (0.35, 0.60)
CRIZ v. ALECT (300 BID)	1	NA	0.34 (0.17, 0.69)
CRIZ v. BRIG	1	NA	0.49 (0.33, 0.73)
ALECT v. CHEMO	1	NA	0.32 (0.17, 0.60)

ALE = alectinib, BID = twice daily, CER = ceritinib, CHEMO = chemotherapy, CI = credible interval, CRIZ = crizotinib, NA = not applicable, QD = once daily.
*Fixed-effects model

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 36: NMA results for all participants: PFS

Table 5. Network meta-analysis of hazard ratios for progression-free survival for individual ALK inhibitors among all patients (experienced and naïve) with ALK-positive non-small cell lung cancer.

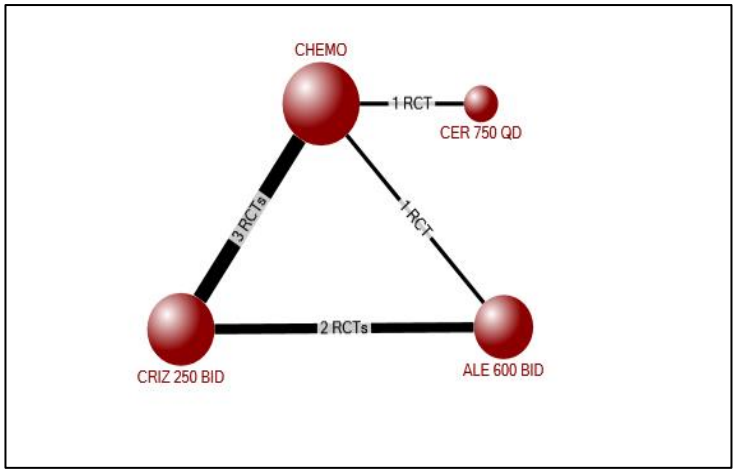
	Hazard ratio (95% credible interval)*					
	CHEMO	CRIZ 250 BID	CER 750 QD	ALE 300 BID	ALE 600 BID	BRIG 180 QD
CRIZ 250 BID	0.46 (0.39, 0.54)	—				
CER 750 QD	0.52 (0.42, 0.64)	1.13 (0.87, 1.47)	—			
ALE 300 BID	0.16 (0.08, 0.33)	0.34 (0.17, 0.70)	0.30 (0.14, 0.64)	—		
ALE 600 BID	0.23 (0.17, 0.30)	0.49 (0.38, 0.63)	0.43 (0.31, 0.62)	1.44 (0.67, 3.05)	—	
BRIG 180 QD	0.23 (0.15, 0.35)	0.49 (0.33, 0.73)	0.43 (0.27, 0.70)	1.44 (0.63, 3.25)	1.00 (0.62, 1.61)	—

ALE = alectinib, BID = twice daily, BRIG = brigatinib, CER = ceritinib, CHEMO = chemotherapy, CRIZ = crizotinib, QD = once daily.
*Fixed-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment). White indicates no significant difference between treatments.

https://doi.org/10.1371/journal.pone.0229179.t005

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Figure 30: Network of trials for SAEs



Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 37: Meta-analysis of each treatment pair included in the evidence network (direct evidence); All participants, Serious adverse events

Comparison	No. of studies	I^2 (%)	Odds ratio (95%CrI)*
CRIZ 250 BID v. CHEMO	3	69	2.11 (1.57, 2.85)
CERT 750 QD v. CHEMO	2	18	1.25 (0.90, 1.75)
CRIZ 250 BID v. ALECT 600 BID	2	50	0.80 (0.52, 1.21)
ALECT 600 BID v. CHEMO	1	NA	1.32 (0.43, 4.07)

ALE = alectinib, BID = twice daily, CER = ceritinib, CHEMO = chemotherapy, CrI = credible interval, CRIZ = crizotinib, NA = not applicable, QD = once daily.
*Fixed-effects model

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

Table 38: NMA results for all participants: SAEs

	Relative risk (95% credible interval); Odds ratio (95% credible interval)			
	CHEMO	**CRIZ 250 BID**	**CER 750 QD**	**ALE 600 BID**
CRIZ 250 BID	**1.66 (1.36, 2.02); 2.08 (1.56, 2.79);**	–		
CER 750 QD	1.18 (0.92, 1.49) 1.25 (0.90-1.74)	**0.72 (0.52, 0.95); 0.60 (0.39, 0.93)**	–	
ALE 600 BID	**1.40 (1.00, 1.92);** 1.60 (1.00, 2.58)	0.85 (0.64, 1.09); 0.77 (0.52, 1.15)	1.19 (0.79, 1.77); 1.29 (0.72, 2.30)	–

Source: Elliott J et al. ALK inhibitors for non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029857/. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner[12]

ALE = alectinib, BID = twice daily, CER = ceritinib, CHEMO = chemotherapy, CRIZ = crizotinib.
*Fixed-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Critical Appraisal

Table 39 summarizes the critical appraisal of the NMA using the International Society for Pharmacoeconomics and Outcomes (ISPOR) criteria.[73] The principal limitations of the NMA concern dearth of RCTs (only 8-10 per NMA) available on ALK-inhibitors for NSCLC and the fact that cross-over was allowed after disease progression in half of the included RCTs, which could have confounded the results for OS and was unable to be adjusted for due to the lack of IPD available. Furthermore, differences were observed in the baseline brain CNS metastases, yet this was not adjusted for in additional analyses. Furthermore, OS data was immature for the alectinib versus brigatinib comparison. PFS is a surrogate outcome for OS and may be prone to measurement error and bias. Indeed, most RCTs that reported PFS employed an independent review committee to ascertain disease progression, yet three RCTs used unblinded assessment as per the trial investigators. Another limitation is that due to the small number of included trials, publication bias was not assessed. These limitations result in imprecision of estimates and uncertainty of results.

Table 39: ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis‡

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes, the population is relevant to this patient population.
2. Are any critical interventions missing?	No, all of the available interventions that would be available to this patient population in Canada were included.
3. Are any relevant outcomes missing?	**Yes**, health-related quality of life is an important outcome that was not included.
4. In the context (e.g., settings and circumstances) applicable to your population?	Yes, this is a relevant setting and context to patients in Canada.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes, a methodologically rigorous systematic review was conducted, including a comprehensive literature search of published and unpublished literature.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes, and these are presented in this section.
7. Is it apparent that poor quality studies were included thereby leading to bias?	Although there were some issues with the included trials, such as occurrence of cross-over and lack of reporting on allocation concealment and randomization, these were deemed not of concern.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	This was an issue for only two of the 13 included RCTs
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Many characteristics were balanced across the trials. However, the ademocarcinoma variable differed for an RCT that enrolled a larger percentage of patients with squamous NSCLC compared to the other trials. Furthermore, variation in the baseline brain CNS metastases was observed across the trials.
10. If yes (i.e., there are such systematic differences in treatment effect), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes, the transitivity assumption was assessed prior to conducting NMA.

ISPOR Questions	Details and Comments
11. Were statistical methods used that preserve within-study randomization?	Yes, Bayesian NMA was performed in WinBUGS, preserving within-study randomization
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Yes, the consistency model was a better fit for the data than the inconsistency model.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes, the WinBUGS program ensures that both direct and indirect evidence are included in the NMA.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes, sub-group analyses were conducted for treatment-naïve compared to those who received previous treatment. However, sub-group analysis was not conducted for baseline brain CNS metastases.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Yes, the fixed effect model had a better fit according to the deviance information criterion so was used instead of the random effects model.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	N/A, a fixed effect model was used.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	Yes, sub-group analyses were conducted for treatment-naïve compared to those who received previous treatment. However, sub-group analysis was not conducted for baseline brain CNS metastases.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes, network diagrams were provided.
19. Are the individual study results reported?	Yes, these were provided in the supplementary appendices.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	Yes, both pairwise meta-analyses and NMA were provided.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes, all results from the NMA were provided, including 95% CrIs.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No**
23. Is the impact of important patient characteristics on treatment effects reported?	Yes, subgroup analyses were performed for treatment naïve compared to patients receiving previous treatment. However, sub-group analysis was not conducted for baseline brain CNS metastases.
24. Are the conclusions fair and balanced?	Yes, conclusions are fair and balanced.
25. Were there any potential conflicts of interest?	No
26. If yes, were steps taken to address these?	N/A

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. ‡ Bolded comments are considered a weakness of the ITC.

7.2.3 Summary

Thirteen trials were included in the published NMA of ALK-inhibitors for NSCLC. For OS and PFS no differences were observed between alectinib and brigatinib. Comparisons between alectinib and brigatinib were not available for the other outcomes (treatment-related deaths and SAEs).

The systematic review methods were well-conducted. Some heterogeneity was observed in baseline characteristics across the studies and not all were adjusted for in the analyses. For example, baseline brain CNS metastases varied across the trials, yet this was not adjusted for. Treatment-switching was common across the trials, yet a sub-group analysis was only conducted for treatment-naïve versus treatment-experienced patients. The fixed effect model was selected, due to model fit, which is appropriate. The principal limitations of the NMA concern dearth of RCTs (only 8-10 per NMA) available on ALK-inhibitors for NSCLC and the fact that cross-over was allowed after disease progression in half of the included RCTs, which could have confounded the results for OS and was unable to be adjusted for due to the lack of IPD available. PFS is a surrogate outcome for OS and may be prone to measurement error and bias. Indeed, most RCTs that reported PFS employed an independent review committee to ascertain disease progression, yet three RCTs used unblinded assessment as per the trial investigators. Another limitation is that due to the small number of included trials, publication bias was not assessed. These limitations result in imprecision of estimates and uncertainty of results. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

7.3 Critical Appraisal of the Ando et al.[13] Published Indirect Treatment Comparison Using Network Meta-Analysis

7.3.1 Objective

The available clinical trials did not provide direct evidence of comparative efficacy for all relevant comparators for the economic model and analysis supporting this submission. A recently published NMA[13] was identified through the literature search conducted by the CADTH team that was relevant to the sponsor's submission. The focus of the NMA was to examine the relative effects of brigatinib compared with alectinib among patients with ALK-positive NSCLC with or without CNS metastasis.

7.3.2 Findings

A published NMA that was relevant to the sponsor's submission is described and critically appraised in the sections below.

Methods

Systematic review

The published systematic review was based on searches of PubMed, Cochrane Library, EMBASE, and SCOPUS in January 2020. In addition, the reference lists of retrieved studies were searched. The eligibility criteria for the systematic review are provided in Table 40 and include the following: RCTs including ALK-naïve adult patients aged 18 years or above with a histological or cytological confirmation of advanced or metastatic ALK-positive NSCLC with at least one measurable lesion according to RECIST version 1.1 and an ECOG-PS of 0 to 2 and no previous ALK-targeted treatment. The interventions were brigatinib (180 mg daily after 7-day lead in period of 90 mg daily) and alectinib (600 or 300 mg twice daily). Only studies reporting the following outcomes were included: PFS (primary) or any adverse event grades 3-5.

Table 40: PICOS Eligibility Criteria

PICOS Item	Eligibility Criteria
Population	ALK-naïve adult patients aged 18 years or above with a histological or cytological confirmation of advanced or metastatic ALK-positive NSCLC with at least one measurable lesion according to RECIST version 1.1 and an ECOG-PS of 0 to 2 and no previous ALK-targeted treatment.
Interventions	Brigatinib (180 mg daily after 7-day lead in period of 90 mg daily) and alectinib (600 or 300 mg twice daily).
Comparators	Crizotinib (250 mg BID).
Outcomes	Efficacy outcome: • Progression-free survival Harms outcomes: • AE grade 3-5
Study design	Randomized controlled trials

Source: Ando et al.[13] Abbreviations: ALK+ = anaplastic lymphoma kinase positive; NSCLC = non-small cell lunch cancer.

AE = adverse event; BID = twice a day; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; , PICOS = population, intervention, comparators, outcomes, study design

Regarding the conduct of the systematic review, the protocol was registered in the PROSPERO database and risk of bias was appraised using the Cochrane risk of bias tool. It is unclear how many people screened literature search results, performed data abstraction, or conducted risk of bias appraisal, as these details were not provided.

Methods for indirect treatment comparisons

The NMAs were performed in a Bayesian environment using the OpenBUGs software. A sensitivity analysis was conducted in the frequentist environment in STATA. Point estimates and 95% credible intervals (CrIs) were estimated using the Markov Chain Monte Carlo methods. Non-informative priors were used, and model convergence was assessed using Brooks-Gelman-Rubin statistics. Treatment effects were provided using ORs and HRs and their respective 95% CrIs. Sub-group analysis was planned for patients with baseline CNS brain metastases and a sensitivity analysis was conducted excluding the ALEX trial in Japanese patients. It was not reported whether inconsistency was assessed nor whether they assessed the validity of the transitivity assumption. No other details were provided. The outcomes included in NMA were PFS and grade 3-5 AEs. The following interventions were included in the NMAs for these two outcomes:

- Brigatinib (180 mg daily after 7-day lead in period of 90 mg daily).
- Alectinib (600 or 300 mg twice daily).
- Crizotinib (250 mg BID).

Results

Systematic review results and NMA feasibility assessment

After screening 3,314 citations and 95 full-text articles, three RCTs met the inclusion criteria and were included in the systematic review. Three trials included in the sponsor's ITC submission were included in the systematic review (ALTA-1L[9], ALEX[4]), yet the ALEX trial conducted in Japanese patients was included (J-ALEX[5]) instead of the ASCEND-4 trial[25], which was included in the sponsor's submission.

Trial characteristics

All RCTs included adult ALK-positive patients with locally advanced or metastatic NSCLC. The ALK-inhibitors examined were crizotinib, alectinib, and brigatinib. The inclusion criteria can be found in Table 41. Additional patient characteristics can be found in Table 42.

Table 41: Inclusion criteria of included RCTs

Table 1. Key inclusion criteria of the included studies.

Study	Key Inclusion Criteria
ALTA-1L	• 18 years of age or older • Locally advanced or metastatic ALK-p NSCLC with at least one measurable lesion • No previous ALK-targeted therapy
ALEX	• 18 years of age or older • Locally advanced or metastatic ALK-p NSCLC with at least one measurable lesion • Performance status range of 0–2 • No previous systemic treatment for advanced NSCLC
J-ALEX	• 20 years of age or older • Stage III B, IV, or postoperative, recurrent, ALK-p NSCLC with at least one measurable lesion • Performance status range of 0–2 • ALK-inhibitor-naïve Japanese patients with ALK-p NSCLC • Chemotherapy-naïve or one previous chemotherapy regimen

ALK-p, anaplastic lymphoma kinase (ALK) rearrangement-positive; NSCLC, non-small cell lung cancer.

Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

Table 42: Characteristics of included RCTs

Table 2. Characteristics of studies.

Study	Treatment Arms	*n*	Age (Years): Median (Range)	Female: No. (%)	ECOG PS: No. (%)	Smoking Status: No. (%)	Histological Type: No. (%)	Stage of Disease at Entry: No. (%)	CNS Metastasis: No. (%)
ALTA-1L	Brigatinib 180 mg once daily (7-day run-in period of 90 mg once daily)	137	58 (27–86)	69 (50)	PS0–1: 131 (96) PS2: 6 (4)	Never: 84 (61) Former: 49 (36) Current: 4 (3)	Adeno: 126 (92) Squamous: 4 (3) Other: 7 (4)	III B: 8 (6) IV: 129 (94)	40 (29)
	Crizotinib 250 mg twice daily	138	60 (29–89)	81 (59)	PS0–1: 132 (96) PS2: 6 (4)	Never: 75 (54) Former: 56 (41) Current: 7 (5)	Adeno: 137 (99) Squamous: 0 (0) Other: 1 (1)	III B: 12 (9) IV: 126 (91)	41 (30)
		total, 275							
ALEX	Alectinib 600 mg twice daily	152	58 (25–88)	84 (55)	PS0–1: 142 (93) PS2: 10 (7)	Never: 92 (61) Former: 48 (32) Current: 12 (8)	Adeno: 137 (90) Squamous: 5 (3) Other: 10 (7)	III B: 4 (3) IV: 148 (97)	64 (42)
	Crizotinib 250 mg twice daily	151	54 (18–91)	87 (58)	PS0–1: 141 (93) PS2: 10 (7)	Never: 98 (65) Former: 48 (32) Current: 5 (3)	Adeno: 142 (94) Squamous: 2 (1) Other: 7 (5)	III B: 6 (4) IV: 145 (96)	58 (38)
		total, 303							
J-ALEX	Alectinib 300 mg twice daily	103	61.0 (27–85)	62 (60)	PS0–1: 101 (98) PS2: 2 (2)	Never: 56 (54) Former: 45 (44) Current: 2 (2)	Adeno: 100 (97) Squamous: 2 (2) Other: 1 (1)	III B: 3 (3) IV: 76 (74) postoperative recurrence: 24 (23)	16 (16)
	Crizotinib 250 mg twice daily	104	59.5 (25–84)	63 (61)	PS0–1: 102 (98) PS2: 2 (2)	Never: 61 (59) Former: 40 (38) Current: 3 (3)	Adeno: 103 (99) Squamous: 0 (0) Other: 1 (1)	III B: 3 (3) IV: 75 (72) postoperative recurrence: 26 (25)	31 (30)
		total, 207							

Total *n* = 785 patients; the intention-to-treat (ITT) population included patients who were randomized regardless of whether an intervention was performed. ECOG, Eastern Cooperative Oncology Group; PS, performance status; CNS, central nervous system.

Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

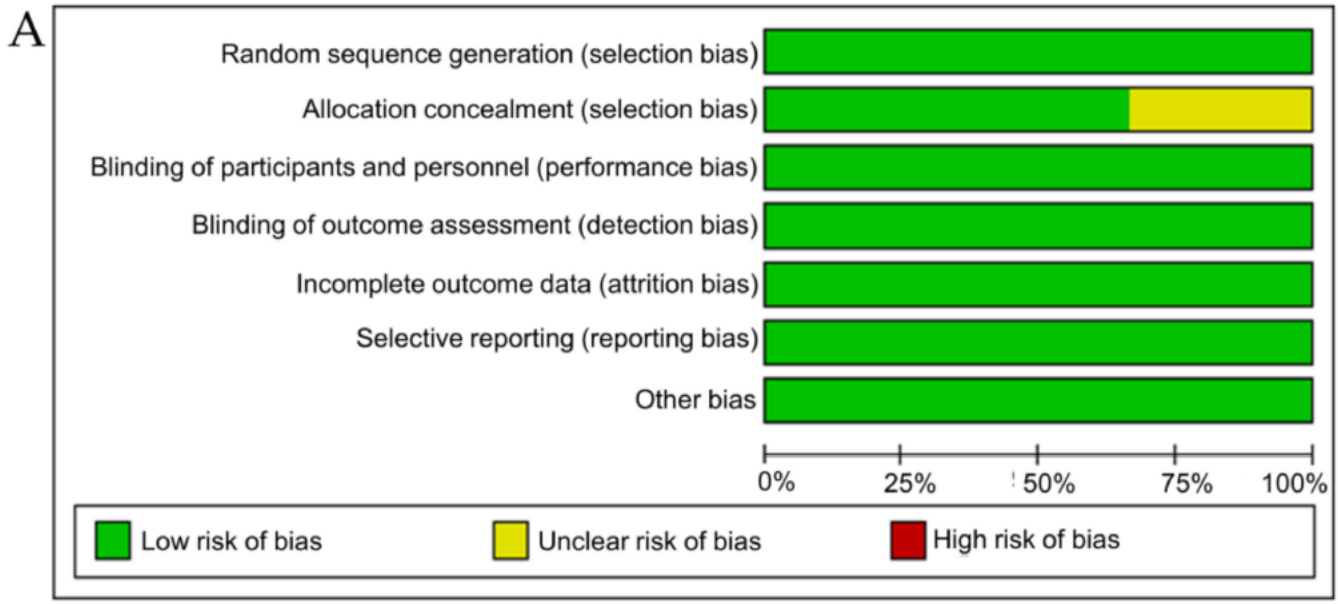
Assessment of Homogeneity

The authors did not report assessing homogeneity prior to conducting NMA.

Risk of Bias

The authors rated all RCTs as having a low risk of bias on the Cochrane tool, with only selection bias as being unclear in one RCT. The risk of bias results are presented in Figure 31.

Figure 31: Risk of bias results



Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

Results of NMA

A network diagram was not provided for any of the outcomes.

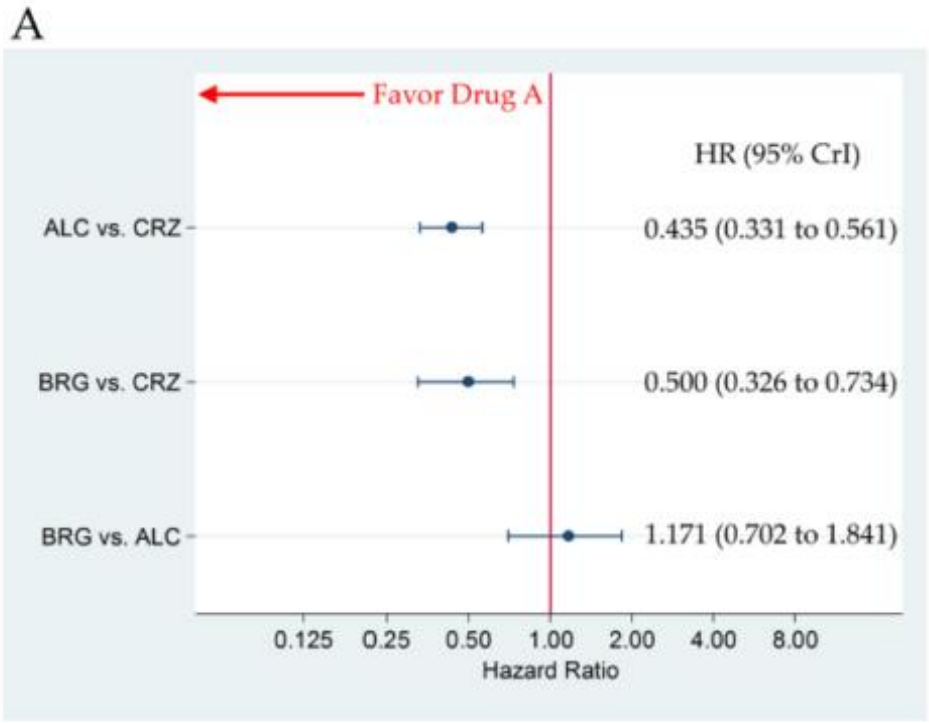
Progression-free survival

For PFS, based on the HRs presented in Figure 32, brigatinib was not favoured over alectinib overall (HR 1.17, 95% CrI: 0.70, 1.84), nor in the sensitivity analysis restricted to patients with CNS metastasis (HR 0.60, 95% CrI: 0.21, 1.36) that is presented in Figure 33. Sensitivity analysis was conducted excluding the J-ALEX trial and the same results were observed (HR 0.56, 95% CrI: 0.20, 1.28). Both brigatinib and alectinib were favoured over crizotinib (brigatinib: HR 0.50, 95% CrI: 0.33, 0.73, CNS HR 0.22, 95% CrI: 0.09, 0.45; alectinib HR 0.44, 95% CrI: 0.33, 0.56, CNS HR 0.38, 95% CrI: 0.24, 0.59) for PFS as well.

Grade 3 and 5 adverse events

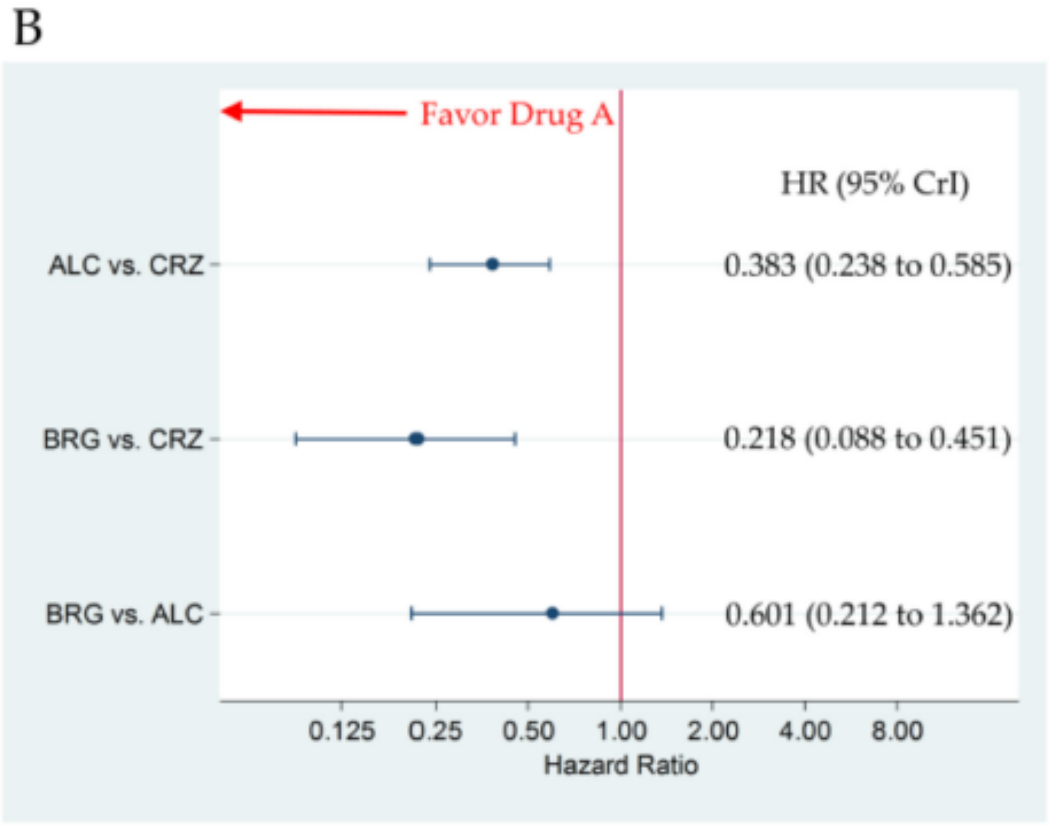
For grade 3 to 5 AEs, based on the ORs, none of the results favoured one ALK-inhibitor over the other (brigatinib versus alectinib OR 1.91, 95% CrI: 0.93, 3.51; brigatinib versus crizotinib OR 1.30, 95% CrI: 0.78, 2.04; alectinib versus crizotinib OR 0.72, 95% CrI: 0.44, 1.11) (Figure 34).

Figure 32: NMA for PFS: Overall results



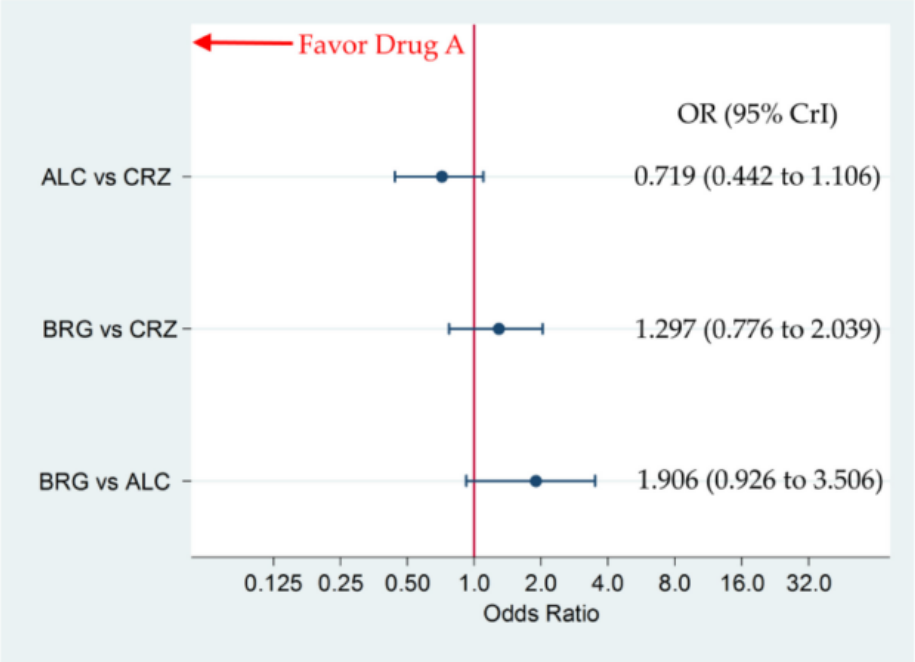
Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

Figure 33: NMA for PFS: Sensitivity analysis by CNS brain metastases



Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

Figure 34: NMA for Grade 3-5 AEs: Overall results



Source: Ando K et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: a systematic review and network meta-analysis. Cancers (Basel). 2020;12(4):942.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7226463/#. Used under Creative Commons license (CC BY 4.0) (Attribution 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[13]

Critical Appraisal

Table 43 summarizes the critical appraisal of the NMA using the International Society for Pharmacoeconomics and Outcomes (ISPOR) criteria[73]. The principal limitations of the NMA concern dearth of RCTs available on ALK-inhibitors, that no closed loops were available to assess consistency, and that other ALK-inhibitors were excluded from the analysis. These limitations result in imprecision of estimates and uncertainty of results. Furthermore, many details were missing from the analysis, including a network diagram, assessment of transitivity, and assessment of heterogeneity.

Table 43: ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis‡

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes, this patient population is relevant to the pCODR submission.
2. Are any critical interventions missing?	**Yes,** other ALK-inhibitors were excluded.
3. Are any relevant outcomes missing?	**Yes,** such as OS and important patient outcomes, such as quality of life.
4. In the context (e.g., settings and circumstances) applicable to your population?	Yes, the context and setting is applicable to the Canadian population.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**No**. Although a comprehensive literature search was conducted, the outcomes were overly restricted, resulting in very few trials being included.

ISPOR Questions	Details and Comments
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes
7. Is it apparent that poor quality studies were included thereby leading to bias?	No, the trials were assessed as having a low risk of bias on most components.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No, the trials were assessed as having a low risk of bias on selective outcome reporting.
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Unclear**, as this was not assessed.
10. If yes (i.e., there are such systematic differences in treatment effect), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Unclear**, as this was not assessed.
11. Were statistical methods used that preserve within-study randomization?	Yes, the OpenBUGS software was used, which preserves within-study randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	N/A, as no closed loops were available
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	N/A
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes, sub-group analyses were conducted by CNS metastasis and another excluding the J-ALEX trial to determine the effects of excluding Japanese patients.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	**None provided.** It did not report whether a fixed or random effects model was used.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**No.** It did not report whether a fixed or random effects model was used.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	Yes, sub-group analyses were conducted by CNS metastasis and another excluding the J-ALEX trial to determine the effects of excluding Japanese patients.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**No,** no network diagrams were provided for the NMAs.
19. Are the individual study results reported?	**No,** no individual study results reported.

ISPOR Questions	Details and Comments
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	**No,** since there were no head-to-head studies reporting on alectinib versus brigatinib, no direct comparisons were available.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes, effect sizes and 95% CrIs were reported.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes, a SUCRA ranking was provided.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes, sub-group analyses were conducted by CNS metastasis and another excluding the J-ALEX trial to determine the effects of excluding Japanese patients.
24. Are the conclusions fair and balanced?	Yes
25. Were there any potential conflicts of interest?	No
26. If yes, were steps taken to address these?	N/A

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. ‡ Bolded comments are considered a weakness of the ITC.

7.3.3 Summary

Three trials were included in the published NMA of ALK-inhibitors for NSCLC. For both PFS and grade 3-5 AEs, no differences were observed between alectinib and brigatinib.

The systematic review methods were unclear, with limitations such as not reporting the number of researchers conducting screening, data abstraction, and risk of bias appraisal. Heterogeneity between the RCTs was not reported, nor was examination of the transitivity assumption. As well, it was not reported whether a random effects or fixed effect model was used. The principal limitations of the NMA concern dearth of RCTs available on ALK-inhibitors, that no closed loops were available to assess consistency, and that other ALK-inhibitors were excluded from the analysis. These limitations result in imprecision of estimates and uncertainty of results. Thus, these limitations must be considered when drawing conclusions based on the results of the NMA.

To compare brigatinib to alectinib, sponsor-submitted ITCs (section 7.1) and two published ITCs (section 7.2 meta-analysis and NMA by Elliott et al. [2020][12] and section 7.3 NMA by Ando et al. [2020][13]) were summarized and critically appraised. For the sponsor-provided ITCs, the results were not statistically significantly difference between brigatinib and alectinib for OS, ORR, PFS, and DOR. The results of the published ITC by Elliott et al.[12] suggested as well, that there was no difference between brigatinib and alectinib for OS and PFS. The published results by Ando et al (2020)[13] were consistent suggesting no statistically significant difference between brigatinib and alectinib for PFS (OS was not reported). In addition, Ando et al. reported that no difference was observed for grade 3 to 5 adverse events between brigatinib and alectinib. The CADTH Methods Team considered the credibility (internal validity) of the comparative estimates to alectinib from the sponsor-provided ITCs to be low. Due to several limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with brigatinib.

With regards to the published ITC, the CADTH Methods Team noted that the Elliott NMA[12] included a well conducted literature search well established NMA methods, comprehensive reporting of methods and results, and was published independently of funding biases. Limitations worth noting in the Elliott NMA is that baseline brain CNS metastases was not controlled for and that cross-over was allowed after disease progression in half of the included RCTs, which could have confounded the results for OS and was unable to be adjusted for due to the lack of IPD available. However, the Elliott NMA conducted a high-quality systematic review and used appropriate statistical analysis to comprehensively compare all available treatments using valid methods.

The CADTH Methods Team identified an additional poster (Lin et al. 2021)[14] which is publicly available on the IASLC 2020 conference website that reported on indirect treatment comparisons of brigatinib compared to other approved ALK inhibitors unspecified or chemotherapy. A systematic review was conducted with literature searches conducted from inception until August 1, 2019 in MEDLINE, Embase, the Cochrane Library and conference proceedings (2016-2019). The eligibility criteria included phase II or III RCTs in ALK inhibitor-naïve ALK-positive NSCLC patients. Bayesian NMA and Bucher ITCs were performed using fixed and random effects models. Overall, 8 RCTs were included assessing alectinib, brigatinib, ceritinib, crizotinib, and chemotherapy and five were global RCTs (undefined; ALEX, ALTA-1L, ASCEND-4, PROFILE 1007, PROFILE 1014). Due to the limited information available from the abstract, the CADTH Methods Team was not able to perform a critical assessment and to provide detailed summaries. While the CADTH Review Team acknowledges receipt of the full NMA report the sponsor was informed about and consented to there being insufficient time to perform a review and critical appraisal of the full report by the CADTH Methods Team within the regular review timelines. The outcomes included in the Lin et al. (2021)[14] abstract included OS and PFS (both independent review assessed and investigator assessed). In addition, sensitivity analysis was reported by no prior chemotherapy and baseline CNS brain metastases for PFS results only. For the OS outcome, no significant differences between brigatinib and all comparators were reported (specific results not reported in the abstract). For brigatinib versus alectinib, no significant differences were observed for independent review assessed PFS (HR, 0.98; 95% CI, 0.61-1.57) or investigator-assessed PFS (HR, 1.01; 95% CI, 0.64-1.58) for overall patients. For the sub-group with no prior chemotherapy, the results were consistent (independent review assessed PFS HR 1.04, 95% CI, 0.62-1.74; investigator assessed PFS HR 0.95 95% Ci, 0.57-1.57). Results were also consistent for the sensitivity analysis restricted to those with baseline brain CNS metastases for investigator-assessed PFS (HR, 0.63 95% CI, 0.28-1.42); results were not provided for this analysis for independent review assessed PFS. Overall, the results for brigatinib versus alectinib that were reported in the Lin et al. (2021)[14] abstract are similar to those:

- provided by the sponsor for PFS as per BICR; unweighted Bucher ITC analysis HR 1.04 (95% CI: 0.65, 1.66), anchored MAIC (HR 0.97, 95% CI: 0.61, 1.55), or unanchored MAIC (HR 0.97, 95% CI: 0.69, 1.38), which was consistent with the investigator confirmed PFS results.
- provided in the Elliott NMA for PFS for the specific doses of brigatinib 180 QD versus alectinib 600 BID (HR 1.00, 95% CrI: 0.62, 1.61). Results of Lin et al.[14] were similar to results of the sub-group analysis by Elliott et al. that was conducted restricted to treatment-naïve patients (brigatinib versus alectinib for PFS: HR 1.07, 95% CrI: 0.66, 1.75), however, the estimates by Elliott directionally favoured alectinib.
- provided in the Ando NMA for PFS (HR 1.17, 95% CrI: 0.70, 1.84), however, the estimates by Ando et al. directionally favoured alectinib. Results were similar in the sensitivity analysis restricted to patients with CNS metastasis (HR 0.60, 95% CrI: 0.21, 1.36).

8 Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Lung Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on brigatinib for NSCLC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. 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.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to 2020 Oct 12); MEDLINE All (1946 to October 12, 2020)

#	Searches	Results
1	(brigatinib* or Alunbrig* or AP26113 or AP-26113 or HYW8DB273J).ti,ab,ot,kf,kw,hw,nm,rn.	1196
2	1 use cctr	82
3	1 use medall	230
4	*brigatinib/ or (brigatinib* or Alunbrig* or AP26113 or AP-26113).ti,ab,kw,dq.	796
5	4 use oemezd	494
6	5 not (conference review or conference abstract).pt.	291
7	3 or 6	521
8	limit 7 to english language	508
9	2 or 8	590
10	remove duplicates from 9	367
11	5 and (conference review or conference abstract).pt.	203
12	limit 11 to english language	203
13	limit 12 to yr="2015 -Current"	183
14	10 or 13	550

2. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

3. **Grey literature search via:**

Clinical trial registries:

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

World Health Organization

http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database

https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trial Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Alunbrig/brigatinib, ALK positive NSCLC

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)

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

Search: Alunbrig/brigatinib, ALK positive NSCLC

Conference abstracts:

American Society of Clinical Oncology (ASCO)

https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

Search: Alunbrig/brigatinib, ALK positive NSCLC — 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).[74]

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

No filters were applied to limit retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 18, 2021.

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).[75] 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, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), 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 CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

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 CADTH 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 CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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