pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Brigatinib (Alunbrig) for Non-Small Cell Lung Cancer

August 1, 2019

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature regarding brigatinib (Alunbrig) for NSCLC conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a 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 on brigatinib (Alunbrig) for NSCLC, a summary of submitted Provincial Advisory Group Input on brigatinib (Alunbrig) for NSCLC, and a summary of submitted Registered Clinician Input on brigatinib (Alunbrig) for NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of brigatinib (Alunbrig) monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC, who have progressed on or who were intolerant to crizotinib.

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 has been issued a Health Canada marketing authorization with conditions, pending the results of trials to verify its clinical benefit. The Health Canada indication reflects the requested patient population for reimbursement: brigatinib is indicated as a monotherapy for the treatment of adult patients with ALK-positive metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib). Note that the Health Canada indication differs slightly from the reimbursement criteria, in that it does not specify 'locally advanced' in its indication.

The recommended dosing regimen 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. Brigatinib should be continued until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

A systematic literature review was conducted to identify studies examining the use of brigatinib as a monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on or who were intolerant to crizotinib. Two relevant ongoing clinical trials were identified which contained data pertaining to the population: The phase 2 ALTA study[1] (n = 222) and the phase 1/2 Study 101 (n= 137).[2] To date, the initial results of both trials have been published in journal articles[1-3] with various subsequent abstracts presented with follow-up data. It is important to highlight that the pCODR requested reimbursement criteria do not exactly align with the patient population in the ALTA trial and Study 101. Whereas the pCODR requested reimbursement criteria include patients who

have progressed on or were intolerant to crizotinib, crizotinib intolerance was not explicitly defined in the ALTA trial and therefore the number of patients who were intolerant to crizotinib could not be confirmed by the submitter. According to the submitter the ALTA trial included crizotinib intolerance based on the investigators' clinical judgement and no data was captured on these patients. In Study 101, 18.2% of patients (25/137) had been previously treated with crizotinib and received brigatinib[4-7] aligned with the current Health Canada approved dosing regimen.[8] Out of 25 patients, only one patient was reported to have stopped crizotinib due to intolerance (with hepatic toxicity).

ALTA phase 2 trial

The ALTA study is an ongoing phase 2 clinical trial evaluating the efficacy and safety of brigatinib monotherapy for the treatment of ALK-positive NSCLC in patients who have progressed on crizotinib.[9] Patients were randomized to receive either 90 mg brigatinib given orally once daily (Arm A; n = 112) or in Arm B (n = 110), 180 mg once daily (with a 7 day lead-in dosing of 90 mg).[1] Patients were stratified based on baseline characteristics of presence of brain metastases and best-response to crizotinib (either CR or PR), as assessed by the investigator.[1] No statistical comparisons were planned between arms A and B with respect to efficacy or safety. Note that this pCODR review will only present the efficacy and safety results from Arm B of ALTA, which is aligned with the Health Canada[8] approved dosing regimen of 180 mg (with the 90 mg lead in).[1] Furthermore, the review team confirmed with the submitter, that Arm B (and not Arm A) provides the relevant dosing for the pCODR requested reimbursement criteria.[1]

The primary outcome of the ALTA trial was confirmed objective response rate (ORR) per response evaluation criteria in solid tumors (RECIST) v1.1 (per investigator). Secondary outcome measures included confirmed ORR as per central independent review committee (IRC), disease control rate (DCR), CNS response as IRC assessed ORR or PFS, duration of response, progression-free survival (PFS), overall survival (OS), safety and tolerability, and patient-reported symptoms of lung cancer and health related quality of life (QoL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-30).[1] The study was conducted across 71 centres located in 18 countries. Patients were recruited into the study from June 4, 2014 to September 21, 2015.[1]

Of the patients recruited into Arm B (n=110), the median age was 56.5 years, with 58.2% females. Of the 110 patients, 69% were white, 27% Asian and 4% of other race. A smoking history was reported in 47 (43%) of individuals. The Eastern Cooperative Oncology Group (ECOG) performance status in Arm B was 0 in 45 (41%), 1 in 56 (51%) and 2 in 9 (8%) of patients enrolled. The majority of patients, 98.2%, had adenocarcinoma and brain metastases were present at baseline in 67.5% of patients.[1] Any prior chemotherapy and more specifically prior platinum-based chemotherapy was received by 73.6% and 72.7% of patients in Arm B, respectively.[6]

For those patients enrolled into Arm B (n=110), the results from the ALTA trial have been analysed, presented or published using data from 4 different data extraction dates: February 29, 2016[1,9,10], May 31, 2016[3,11], February 21, 2017[12-14] and September 29, 2017.[15] The median duration of follow-up as of September 29, 2017 was 24.3 months (0.1-39.2 months) with 32 patients (29.1%) of patients remaining in the study.[6,15]

From the latest analysis date of September 29, 2017,[6,15] the ORR, as assessed by the investigator, was 56.4 % with 5 (4.5%) of patients completely responding and 57 patients (51.8%) with a partial response.[6] The ORR was confirmed by an IRC which determined similar response rates. Progression free survival at the time of the latest analysis was estimated to be 15.6 months (95%CI: 11.1-21.0). For those individuals with asymptomatic

brain metastases at baseline in Arm B of the ALTA trial, at the time of this final analysis the median intracranial PFS was 18.4 months (95%CI: 12.6-23.9).[15,16] The median overall survival was determined to be 34.1 months (95%CI: 27.1-nr) with a 1-year probability of survival of 80% (95%CI: 71-87).[6,15,16]

Quality of life measurements were available from the initial study report as measured by the EORTC-QLQ-30.[1,10] HRQoL was measured monthly, increased up to 7 months following initiation of therapy and then declined. However, the mean values remained above the baseline mean although there were increasingly fewer patients with less than 50% of the patients providing QLQ-C30 scores at cycle 10 and beyond.[1,9,10]

Data related to adverse events (AEs) were available for the February 21, 2017 and the September 29, 2017 data cuts. Information for the February 21, 2017 data cut was made available by the submitter.[17] In the ALTA trial Arm B, all patients (100%) experienced at least one AE. Of these AEs, 72 patients (65.5%) had a Grade 3 severity or greater AE with serious treatment-emergent adverse events (TEAE) occurring in 50.9% of patients. Twenty patients (18.2%) experienced a serious treatment related TEAE.[17] Treatment doses of brigatinib were reduced in 30% of patients and 59.1% had a dose interruption related to a TEAE. Therapy was discontinued in 10.9% (12 patients) secondary to a TEAE.[17]

For patients treated with a dose of 180 mg daily with a 7-day lead-in, AEs leading to death within 30 days of the last dose or related to the study drug were reported for both studies together (ALTA trial [Arm B; N = 110] and Study 101 [N = 25]); 12 patients (8.7%) out of 138 experienced at least one of these AEs. The causes of these AEs were listed as: neoplasm progression in 8 (5.8%) patients, and pneumonia, sudden death, hydrocephalus, and urosepsis in one patient (0.7%) each.[17]

Further information regarding Grade 3 or greater TEAE were reported in a poster by Huber et al. using data from the September 29, 2017 data cut.[15,16] In Arm B of the ALTA trial, based on this latest data analysis, the following Grade 3 or greater TEAE occurred (in ≥3% of patients): increased blood creatine phosphokinase (13%), hypertension (5%), increased lipase (5%), rash (4%), pneumonitis (4%), increased aspartate aminotransferase (4%), increased aspartate aminotransferase (3%), hyponatremia (3%), nausea (1%), and increased amylase (2%).[15,16]

Presented in Table 1.1 are the highlights of the key outcomes of the ALTA trial from the primary published analysis and data available from the various data extractions.

Table 1.1: Highlights of Key Outcomes ALTA Phase 2 Trial

	ALTA Trial Arm B (N=110)			
Efficacy Outcomes				
Primary Source	Kim et al. 2017,[1,10] ClinicalTrials.gov[9]	Ahn M-J et al. 2017[11]	Ahn M-J et al. 2017,[12,18] Hochmair et al. 2018[14]	EMA Report, 2018[6] Huber et al. 2018[15,16]
Data cut-off date	February 29, 2016	May 31, 2016	February 21, 2017	September 29, 2017
Median Duration of Follow-up, Months (range)	8.3 (0.1-20.2)	11.0 (na)	18.6 (0.1-32.0)	24.3 (0.1-39.2)
Median Duration of Treatment, Months (range)	8.4 (na)	na	na	17.1 (0.07-39.2)
Patients remaining on treatment, n (%)	76 (69)	62 (56)	45 (41)	32 (29)
Primary Outcome - confirmed ORR by investigator assessment				
Investigator-assessed ORR No. (%) (97.5%CI)	59 (54) (43-65)	60 (55) (44-65)	60 (55) (44-66)	62 (56.4)(45.2-67.0)
Complete, n (%)	4 (4)	na	(5)	5 (4.5)
Partial, n (%)	55 (50)	na	(51)	57 (51.8)
Key Secondary Outcomes				
Confirmed ORR - independent review committee (IRC)				
Confirmed ORR No. (%) (95%CI)	58 (53) (43-62)	59 (54) (44-63)	(55) (45-64)	62 (56.4) (46.6-65.8)
Complete, n (%)	5 (5)	na	(5)	6 (5.5)
Partial, n (%)	53 (48)	na	(49)	56 (50.9)
PFS				
PFS - Investigator assessed, Median Months (95%CI)	12.9 (11.1-nr)	15.6 (11.1-nr)	15.6 (11.1-19.4)	15.6 (11.1-21.0)
1-Year Overall PFS, Probability % (95%CI)	na			58 (47-67)
PFS-IRC, Median Months (95%CI)	15.6 (11.0-nr)	15.6 (11.6-nr)	16.7 (11.6-nr)	16.7 (11.6-21.4)
OS				
Median OS (95%CI) months	na	na	27.6 (27.6-nr)	34.1 (27.1-nr)
1-Year Overall Survival, Probability % (95%CI)	80 (67-88)	82 (72-88)	80 (71-87)	80 (71-87)
2-Year Overall Survival, Probability % (95%CI)				66 (56-74)
QoL				
EORTC QLQ-C30 baseline, Mean (SD)	58.49 (23.40)	na	na	na
EORTC QLQ-C30 cycle 7, Mean (SD) (N=76)	71.05 (19.88)	na	na	na
Harms Outcome,			Safety Report[17]	
Grade ≥3 overall, n (%)	na	na	72 (65.5)	na
AE (any grade), n (%)	na	na	110 (100)	na
Serious TEAE, n (%)	na	na	56 (50.9)	na
Serious Treatment-Related TEAE, n (%)	na	na	20 (18.2)	na
TEAE - Dose reduction, n (%)	22 (20)	25 (23)	33 (30.0)	32 (29)
TEAE - Dose interruption, n (%)	40 (36)	na	65 (59.1)	68 (62)
WDAE	nr	11 (10)	12 (10.9)	12 (11)
Abbreviations: AE - adverse events; CI - confidence interval; CR - complete response; EORTC QLQ - European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire; na - not available; nr				

	ALTA Trial Arm B (N=110)
- not reported; OR - odds ratio; ORR - overall response rate; OS - overall survival, PFS - progression-free survival; PR - partial response; QOL -health-related quality of life; TEAE - Treatment-emergent adverse event; WDAE - Withdrawal due to adverse event.	

101 phase ½ trial[2]

The Study 101 was a multiple arm phase I/2 dose ranging trial.[2] In phase 1 of this study the dose for brigatinib was escalated with a starting dose of 30 mg up to total daily dose of 300 mg. The expansion phase of the study administered brigatinib in two regimens, 90 mg once daily and 180 mg once daily with a 7-day lead in period of 90 mg. Study 101 recruited 137 patients.[2] Only 18.2% of patients (25/137) enrolled in the study had been previously treated with crizotinib and received brigatinib,[4-7] aligned with the current Health Canada approved dosing regimen of 180 mg with a 7-day lead-in of 90 mg.[8] Data, where available, for this subgroup of patients from Study 101 are presented in this review. The evaluation of these patients from Study 101 is a post-hoc analysis and was not initially presented in the primary publication.[2,19] Safety and tolerability data for these 25 patients, who were previously treated with crizotinib, were not published. Upon request, data which included the subgroup of 25 patients plus 3 individuals who were crizotinib naïve with ALK+NSCLC, was made available from the submitter with a data cut-off of February 21, 2017.[17]

The primary outcome of the Study 101 for the expansion phase of the study was investigator assessed objective response rate (ORR) per RECIST v1.1 (per investigator), defined as the sum of the proportion of patients with partial response and complete response.[2] Secondary outcome measures included ORR by IRC, PFS, OS, best target lesion response, best overall response, duration of response, safety and tolerability. Only selected outcomes were reported for the subgroup of interest (N = 25). Although separate primary endpoints were defined in the protocol for the expansion phase, in the efficacy analyses patients from the dose-escalation phase were combined with those from the expansion phase matched on certain criteria such as tumor type, molecular subset and starting dose regimen.[2,19]

The study was conducted across 9 centres located in the US and Spain. Patients were recruited into the study from September 20, 2011 to July 8, 2014.[2] For the cohort of 25 individuals from Study 101, the median age was 57 years, with 44.0% females. Of the 25 patients, 80% were White, 12% Asian and 8% of other race. The ECOG performance status was 0 in 10 (40%) and 1 in 15 (60%) of the patients with none of patients having a performance status of 2. The majority of patients, 96%, had adenocarcinoma and had received prior chemotherapy (68%). Brain metastases were present at baseline in 18 (72%) of patients.[17,20]

Limited information is available regarding treatment outcomes for the Study 101 patients, and is available from published abstracts and an assessment report.[4-7] The investigator assessed ORR for the 25 patients from Study 101, as of the May 31, 2016 analysis, was 80% (95%CI: 59.3-93.2) with complete response in 3 patients (12%) and a partial response in 17 patients (68%).[6] The disease control rate was 88% (95%CI: 68.8-97.5).[6] The PFS was calculated to be 16.3 months (95%CI: 9.2-28.1) as of the February 21, 2017 data extraction with a 1-year probability of PFS of 62% (95%CI: 40-78).[7] Overall survival estimates were also determined as of the last data extraction date. The median OS was 29.5 months (95%CI: 21.4-nr). The estimated probability of 1-year and 2-year survival was 84% and 64%, respectively.[7]

Data related to adverse events were made available from the submitter as of the February 21, 2017 data cut off.[17] From Study 101, data related to all ALK+NSCLC patients receiving

brigatinib according to the Health Canada approved label, independent of their prior crizotinib utilization (N=28) was provided by the Submitter. Of this group 96.4% (n=27) experienced at least 1 TEAE.[8,17] Twenty patients (71.4%) had a Grade 3 severity or greater TEAE with serious TEAE occurring in 42.9% of patients. Three patients (10.7%) experienced a serious treatment related TEAE. Treatment doses of brigatinib were reduced in 21.4% of patients and 53.6% had a dose interruption related to a TEAE. TEAEs leading to treatment discontinuation occurred in 10.7% (3 patients).[17]

Presented in Table 1.2 are the highlights of the key outcomes of Study 101 from the data available from the various data extractions.

Table 1.2: Highlights of Key Outcomes of ALK+NSCLC Study 101 Trial

	Study 101 (N=25)		
Efficacy Outcomes			
Primary Source	Bazhenova LA et al. 2016[5]	Bazhenova LA et al. 2017[4] EMA Report 2018[6]	Bazhenova LA et al. 2017[7]
Data cut-off date	16 Nov 2015	May 31, 2016	February 21, 2017
Median Duration of Follow-up, Months (range)	na	na	na
Patients remaining on treatment, n (%)	na	na	na
Primary Outcome - ORR by investigator assessment			
Investigator-assessed ORR No. (%) (95%CI)	20 (80) (59-93)	20 (80) (59.3-93.2)	na
Complete, n (%)	2 (8)	3 (12)	na
Partial, n (%)	18 (72)	17 (68)	na
Key Secondary Outcomes			
Confirmed ORR No. (%) (95%CI)	19 (76) (55-91)	19 (76) (54.9-90.6)	19 (76) (55-91)
Complete, n (%)	na	na	na
Partial, n (%)	na	na	na
Median Duration of Response in confirmed responders, months (95%CI)	na	na	14.9 (7.9-33.3)
Disease Control Rate n (%) (95%CI	22 (88)	22 (88) (68.8-97.5)	na
PFS			
PFS, Median Months (95%CI)	na	16.3 (9.2-nr)^	16.3 (9.2-28.1)
Probability of PFS at 1 year, % (95%CI)	na	na	62 (40-78)
OS			
Median OS (95%CI) months	na	na	29.5 (21.4-nr)
1-Year Overall Survival, Probability % (95%CI)	na	na	84 (63-94)
2-Year Overall Survival, Probability % (95%CI)	na	na	64 (42-79)
Harms Outcome			Safety Report (N=28)[17]
Grade ≥3 overall, n (%)	na	na	20 (71.4)
AE (any grade), n (%)	na	na	27 (96.4)
Serious TEAE	na	na	12 (42.9)
Serious Treatment Related TEAE, n (%)			3 (10.7)
TEAE - Dose reduction, n (%)	na	na	6 (21.4)
TEAE - Dose interruption, n (%)	na	na	15 (53.6)
WDAE	na	na	3 (10.7)
Abbreviations: AE - adverse events; CI - confidence interval; CR - complete response; na - not available, nr - not reached; ORR - overall response rate; OS - overall survival, PFS - progression-free survival; PR - partial response; SAE - serious adverse event; TEAE - treatment emergent adverse event; WDAE - withdrawal due to adverse event.			

Patients with Brain Metastases

In the ALTA trial an exploratory analysis was completed examining the efficacy and safety of brigatinib in patients with brain asymptomatic metastases at baseline. This analysis is reported primarily in the published papers by Kim et al.[1] and Camidge et al.[3] and additionally in subsequent abstracts[12-16] and reports with updated analyses. The results of these analyses are summarized in Table 1.3 below.

Table 1.3: Highlights of Key Outcomes ALTA Phase 2 Trial in Patients with Asymptomatic Brain Metastases at Baseline

	ALTA Trial Arm B (N=73)			
Efficacy Outcomes				
Primary Source	Kim et al. 2017[1]	Camidge et al. 2018[3]	Ahn M-J et al. 2017,[12] Ou S-H et al. 2017,[13] Hochmair et al. 2018[14]	EMA Report, 2018[6] Huber et al. 2018[15]
Data cut-off date	February 29, 2016	May 31, 2016	February 21, 2017	September 29, 2017
Median Duration of Follow-up, Months (range)	na	10.5 (2-21.1)	na	na
Patients remaining on treatment, n (%)	na	40 (55)	29 (40)	na
Primary Outcome - ORR by investigator assessment				
Investigator-assessed ORR No. (%) (95%CI)	na	43 (59) (47-70)	na	na
Complete, n (%)	na	na	na	na
Partial, n (%)	na	na	na	na
Key Secondary Outcomes				
ORR - independent review committee (IRC)				
Confirmed ORR No. (%) (95%CI)	na	na	na	na
Complete, n (%)	na	na	na	na
Partial, n (%)	na	na	na	na
PFS				
PFS, Median Months (95%CI)	na	12.9 (9.3-nr)	na	na
OS				
Median OS (95%CI) months	na	nr (17.8-nr)	na	na
1-Year Overall Survival, Probability % (95%CI)	na	85 (73-92)	na	na
Duration of Intracranial Response (DOIR), Months (95%CI)	nr (5.6-nr)	nr (9.3-nr)	16.6	16.6 (3.7-nr) (n=12)
IRC-assessed intracranial PFS, Median Months (95%CI)	12.8 (11.0-nr)	18.4 (12.8-nr)	18.4 (12.6-nr)	18.4 (12.6-23.9)
Patients with any measurable brain metastases (N=18)				
Confirmed Cranial Response Rate OCRR No. (%) (95%CI)	12 (67) (41-87)	12 (67) (41-87)	12 (67) (41-87)	12 (67) (41-87)
Complete, N (%)	0	0	na	na
Partial, N (%)	12 (67)	12 (67)	na	na
Intracranial Disease Control Rate (IDCR) N (%) (95%CI)	15 (83) (59-96)	15 (83) (59-96)	(83) (59-96)	(83) (59-96)
Patients with only non-measurable brain metastases (N=55)				
Confirmed Cranial OCRR No. (%) (95%CI)	10 (18) (9-31)	10 (18) (9-31)	10 (18) (9.1-30.9)*	na
Complete, N (%)	10 (18)	10 (18)	10 (18)	na
Intracranial Disease Control Rate (IDCR) N (%) (95%CI)	na	47 (85) (73-94)	na	47 (85) (73-94)
Harms Outcome				
Grade ≥3 overall, n (%)	na	36 (49)	na	na

	ALTA Trial Arm B (N=73)			
AE (any grade), n (%)	na	73 (100)	na	na
Serious TEAE	na	28 (38)	na	na
Serious Treatment Related TEAE, n (%)	na	na	na	na
TEAE - Dose reduction, n (%)	na	13 (18)	na	na
TEAE - Dose interruption, n (%)	na	28 (38)	na	na
WDAE	na	7 (10)	na	na

Abbreviations: AE - adverse events; CI - confidence interval; CR - complete response; DOIR - duration of intracranial response; IDCR - intracranial disease control rate; IRC - independent review committee; na - not available; nr - not reported; OCRR - objectively confirmed response rate; OR - odds ratio; ORR - overall response rate; OS - overall survival, PFS - progression-free survival; PR - partial response; TEAE - Treatment-emergent adverse event; WDAE - Withdrawal due to adverse event.

Limitations/Sources of Bias

- The Study 101 was an open label phase 1/2 trial with no active treatment or placebo control groups that was conducted to evaluate the initial safety, tolerability, pharmacokinetics (PK) profile, and preliminary anti-tumor activity of brigatinib in patients with advanced malignancies including NSCLC patients with ALK rearrangements. Therefore, the intent of the study was not to draw conclusions on efficacy as it was a dose finding study.

- The analysis of data from the subgroup of 25 patients of interest from Study 101 should be regarded as exploratory as it was not part of the original study protocol and was not presented in the initial clinical trial publication.[2] Within Study 101, patients were not randomized to a specific dosing regimen but were assigned in a step-wise fashion in Phase 2, which could result in allocation bias by the clinicians and research staff.[2]

- The ALTA study is an ongoing phase 2 clinical trial with no active treatment or placebo control groups. Randomized comparisons between the study treatment (brigatinib) and its potential comparators currently available in this setting are needed to justify the observed clinical efficacy and safety outcomes. Although brigatinib resulted in clinical and survival benefits, no conclusions could be made regarding the efficacy of this drug relative to currently used treatment options for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

  In their feedback to the initial recommendation, one of the registered clinicians noted that the sample size of each of the ALTA arms [arm A, n = 112, 90 mg brigatinib once daily; and arm B, n = 110, 180 mg once daily with the 90 mg lead in] is 40-50% larger than the alectinib arm [n = 72] from the phase III ALUR trial; and even ALTA's inferior arm A had a PFS [IRC-assessed PFS 9.2 months (95%CI: 7.4-12.8)] that was better than the best results observed with alectinib in second line [e.g., ALUR trial[39] IRC-assessed PFS 7.1 months (95%CI: 6.3-10.8); or pooled analysis[116] of the alectinib phase II studies (alectinib NP28673 and NP28761) IRC-assessed PFS 8.3 (95%CI: 7.0-11.3)]. It was noted that the larger sample size observed in the ALTA trial would serve to reduce the uncertainty in the efficacy estimates derived from the phase II ALTA trial. In response to the registered clinician's feedback, the pCODR Methods Team noted that notwithstanding a relatively large sample size in the ALTA trial and observed PFS benefit, ALTA was a

non-comparative phase II trial and no conclusions can be made regarding the efficacy of this drug relative to currently used treatment options. In addition, it is important to note that the primary objective of phase II (non-randomized or randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase III trials. The purpose of phase II trials is not to provide definitive estimates of efficacy. In order to make a direct comparison between ALK inhibitors, head-to-head RCT data is required, as is currently being conducted in the randomized phase III ALTA 3 trial (NCT03596866)[111].

In their feedback to the initial recommendation, the submitter noted that there is evidence to suggest that the ALK+ NSCLC patient populations enrolled in clinical trials is generalizable to the real-world setting. In two real world studies[112,113] investigating ALK+ NSCLC patient populations, the baseline characteristics, such as age and rates of never-smokers, were very similar to those in the 13 clinical trials enrolling ALK+ NSCLC patients. In addition, brigatinib's phase III, second-line post-crizotinib study (ALTA 3 trial)[111] is currently enrolling patients and the anticipated completion is August 2021. This timing coincides with interim data availability from the CARMA[114]/CARMAC[115] real world studies which will help bring certainty to the results observed in ALTA and ALTA 3 studies in the real-world setting. In response to the submitter's feedback, the pCODR Methods Team noted that, while the real world studies by Hochmair et al. (2018)[112] and Gomet et al (2018)[113] were identified by the pCODR systematic literature search that was conducted as part of the evidence assessment for this submission, they were excluded based on their type of study design; case series or retrospective design, which did not meet the selection criteria of this pCODR review. CARMA[114] is an observational study and CARMAC[115] is a retrospective chart review. Both studies are currently ongoing and no data are currenlty available.

- Due to the open-label design, the study investigators and patients are aware of the treatment status, which may increase the possibility of detection bias and performance bias. Biases associated with the open-label design were addressed through the implementation of an IRC, however, this adjudication was not used as the primary outcome measure for the trials, which relied upon the investigator-assessed efficacy.[1,2] In addition, subjective outcomes (i.e. AEs and QoL) may also be biased as a result of the open-label design.

- Survival estimates and quality of life measurements should also be interpreted with caution due to attrition in the study, with a limited number of participants remaining on trial following 12 months of follow-up.

- Exploratory statistical analyses were completed for sub-group analyses and long-term follow-up data cuts. Longitudinal evaluations were not stated in the study publications and no statistical adjustment was made for the repeated analysis of outcome measures.

- The safety data provided by the Submitter for the Study 101 includes information on 3 additional patients from the study that were naïve to crizotinib, however, the AEs rates reported with the larger group (N=28) are aligned with the ALTA trial results for the same dosing regimen in Arm B.[1,17]

- Both studies were funded by the sponsor with staff and representatives involved in all aspects of the conduct of the trial with the potential of conflict of interest and reduced objectivity related to the reporting and interpretation of the findings.

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

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input on brigatinib for the treatment of adult patients with anaplastic lymphoma kinase positive (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

From the patient's perspective, the impact of a lung cancer diagnosis can leave patients completely shattered and overwhelmed causing them to worry about available treatment options, survival and their loved ones. LCC noted that for patients with ALK-positive disease, just knowing there is treatment targeted to their mutation gives them hope and the ability to face each day with positivity. OLA reported that some of the symptoms related to lung cancer include extreme fatigue and exhaustion, weakness, breathing difficulties (such as shortness of breath), cough, and pain. Symptoms change frequently, which impacts daily activities, day-to-day planning, and can be challenging to manage. OLA also highlighted that lung cancer negatively impacts patients' relationships with family and friends, independence, emotional well-being, and financial situation, resulting in a significant emotional toll followed by depression. In addition, OLA noted that several patients stated the need for clearer communication and information regarding their disease and available treatment options in order to cope with their condition and to plan out next steps.

Current therapies for 2nd line treatment after progression on crizotinib include chemotherapy or chemoradiation, ceritinib, and alectinib. As reported by the LCC, chemotherapy has many side effects that interfere with daily activities as well as require multiple, and often quite long, hospital visits for intravenous infusions. Though not all patients will experience toxicities, the prospect of going on chemotherapy is devastating to patients. Patients receiving treatment with ceritinib on the other hand described the experience as a continuation of hope, with patients being able to maintain a high level of functioning and active lives. Side effects were reported to be manageable, and many patients achieved control of their cancer, including brain metastases. Patients that received alectinib also saw a reduction in tumor size and lung cancer symptoms. Given that ceritinib and alectinib are oral treatments, patients and their caregivers were not burdened or inconvenienced with long hospital visits or recuperation time.

In terms of expectations for alternative treatment options LCC noted that focus was placed on manageable side effects and extension of life and quality of life. More specifically patients' expectations included: the ability to maintain a high level of functionality, to continue to parent, to work, to maintain family life, and to enjoy life (e.g., travel and go on vacation). LCC also highlighted the importance of new and better treatments that provide the opportunity to extend survival, give patients hope for the future, and provide time to wait for new treatment options. OLA reported that overall patients desire treatments that will increase independence, require less assistance from others, and improve energy. More specifically patients' expectations included: stopping or slowing the disease progression, reducing side effects, maintaining quality of life,

administering of treatments at home, and having less or no cost burden associate with the new treatment.

LCC provided the perspective of 5 patients and 4 caregivers with experience with brigatinib. According to LCC three key themes emerged from the patient experience with brigatinib: (i) it was effective in controlling cancer (including brain metastases), (ii) it had manageable side effects, and (iii) it allowed patients to have a good quality of life. In particular patients reported that brigatinib led to stable disease, reduced or eliminated brain metastases, overcame disease resistance to crizotinib and allowed continuation of an active life style. Common side effects of brigatinib included fatigue, vomiting, diarrhea, constipation, abdominal pain, and muscle and joint paint. A few patients indicated that, compared with crizotinib, they had better tolerated brigatinib with fewer side effects. LCC indicated that patients were able to continue an active life style while receiving brigatinib.

Provincial Advisory Group (PAG) Input

Input was obtained from the eight of the 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:

- Indication creep into first-line treatment
- Comparative data to ceritinib as well as alectinib

Economic factors:

- Additional costs to manage and treat adverse events

Registered Clinician Input

pCODR received two group clinician inputs (representing 9 clinicians) on brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK tyrosine kinase inhibitor (TKI) (crizotinib). A joint input from seven oncologists from Lung Cancer Canada (LCC) and two oncologists from Cancer Care Ontario (CCO) was submitted.

The clinicians providing input noted that for the present indication, the most relevant comparators to brigatinib would be ceritinib or alectinib (the latter depending on availability). It was also noted by clinicians from the LCC that in provinces where ceritinib is not funded, the current standard of care is platinum-based doublet therapy. The clinicians from both groups agreed that the eligible patient population in clinical practice aligns with the patient population in the ALTA trial. Clinicians from LCC further suggested that brigatinib would be an excellent alternative in patients who are intolerant to crizotinib. According to the clinicians from LCC, brigatinib addresses an unmet need in the target population as alternative therapies for second-line treatment following progression on crizotinib provide smaller gains in progression-free survival (PFS) than brigatinib. The clinicians from CCO noted that the present unmet need will be addressed once alectinib is available. This group indicated that once alectinib is available, most clinicians will chose alectinib as 1st line therapy or post progression on crizotinib. Clinicians from LCC reported their clinical experience of using brigatinib after crizotinib, which showed favourable PFS and toxicity results compared with their institutional experience of using ceritinib after

crizotinib. There was some discrepancy between the clinician groups regarding the sequencing of current drugs for the treatment of locally advanced or metastatic NSCLC. The LCC group indicated that brigatinib would replace ceritinib as second-line treatment after crizotinib unless otherwise contraindicated. This group further noted that each of the ALK TKIs have specific toxicity profiles, and thus have potential benefit and roles depending on patient comorbidities and specific circumstances. The clinicians from CCO indicated first-line preference as alectinib or ceritinib. This group further noted that brigatinib, ceritinib, or alectinib are options in second-line, however, there is currently insufficient evidence to recommend one over the other.

Summary of Supplemental Questions

A manufacturer-submitted ITC which compared brigatinib to alectinib, ceritinib, chemotherapy, crizotinib retreatment, and best supportive care for patients with ALK+ NSCLC who progressed on crizotinib was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[20,21] The unanchored MAICs found that brigatinib statistically significantly improved PFS compared to ceritinib, alectinib, and chemotherapy, but no difference was found with crizotinib retreatment. Brigatinib also statistically significantly improved OS compared with ceritinib and crizotinib retreatment, but results were inconsistent when compared with alectinib and chemotherapy. No difference was found when brigatinib was compared to ceritinib or chemotherapy for discontinuation due to adverse events, and inconsistent results were seen when compared with alectinib. Brigatinib was associated with a lower likelihood of Grade 3 or 4 adverse events compared to alectinib; no difference was found when comparing brigatinib to ceritinib, and inconsistent results were seen when compared to chemotherapy. Health-related quality of life data were not reported. Concerns were noted related to the internal validity of the results. The main limitations of the ITC included the use of unanchored MAICs, given the likelihood of bias due to missing prognostic factors and effect modifiers. The use of unanchored MAICs as head-to-head studies in the NMAs is a serious limitation of the NMAs, along with the double-counting of patients on brigatinib resulting in falsely improved precision in the NMAs. Because if these limitations, the unanchored MAIC estimates are most appropriate for the economic analysis, however, the comparative efficacy and safety estimates obtained are likely biased due to these limitations, 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.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR 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 1.4 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 1.4: Assessment of generalizability of evidence for brigatinib

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Performance status</td><td><u>ALTA 201 phase 2 trial (Arm B):</u>
Patients were included in the trial if they had ECOG status of ≤ 2.
<table>
<tr><th>ECOG</th><th>Arm B, 180 mg once daily (with lead-in) (N=110)[1]</th></tr>
<tr><td>0, N (%)</td><td>45 (41)</td></tr>
<tr><td>1, N (%)</td><td>56 (51)</td></tr>
<tr><td>2, N (%)</td><td>9 (8)</td></tr>
</table>
<u>101 phase ½ trial (N=25):</u>
Patients were included in the trial if they had ECOG performance status 0 or 1.
<table>
<tr><th>ECOG</th><th>N (%)</th></tr>
<tr><td>0</td><td>10 (40)</td></tr>
<tr><td>1</td><td>15 (60)</td></tr>
</table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The majority of patients enrolled in the trial had an ECOG PS of 0-1. Data on the efficacy and safety of brigatinib in patients with an ECOG PS >1 was limited. Although there was a low proportion of patients with ECOG PS 2, the CGP agree that the use of brigatinib in patients with ECOG PS ≥2 may be appropriate and should be left to the discretion of the treating oncologist.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>CNS metastasis</td><td><u>ALTA 201 phase 2 trial:</u>
Arm B (N = 110):
<table><tr><th colspan="2">CNS metastases at baseline (measureable and non-measureable), N = 73 (67%)</th></tr><tr><td>Confirmed ORR* (investigator-assessed) N (%) (95%CI)</td><td>643
43 (59) (47-70)</td></tr><tr><td>Disease control rate N (%) (95%CI)</td><td>63 (86.3) (76.2-93.2)</td></tr><tr><td>Probability of OS at 1 year % (95% CI)</td><td>85 (73-92)</td></tr><tr><td colspan="2">*Confirmed ORR (confirmed ≥ 4 weeks after initial response).</td></tr></table>Exclusion criteria: Patients who had symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids.
<u>101 phase ½ trial</u>:
Not available</td><td>Are the results of the trials generalizable to patients who have progressed on crizotinib and have CNS metastases?</td><td>The benefit of brigatinib in patients with CNS metastases is demonstrated by the RR and the duration of response. This includes those with CNS metastasis at initial presentation, those who developed CNS disease on first-line crizotinib or other systemic therapies.</td></tr>
<tr><td></td><td>Age</td><td><u>ALTA 201 phase 2 trial:</u>
201 trial enrolled patients aged 18 years or older.
<table><tr><th colspan="2">Arm B, 180 mg once daily (with lead-in) (N=110)[1]</th></tr><tr><td>Median age (range)</td><td>56.5 (20-81)</td></tr><tr><td colspan="2">ALL Patients (Arms A + B) (N = 222</td></tr><tr><td>18 - 64</td><td>170 (76)</td></tr><tr><td>>65</td><td>52 (23)</td></tr></table><u>101 phase ½ trial (N=25):</u>
Not available</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>ALK-positive NSCLC patients tend to be younger at the age of diagnosis. The CGP noted that the trial enrolled patients aged 18 years or older. The CGP recognizes that the proportion of patients ≥65 years in the trial was small. However, the CGP agree that the use of brigatinib may be appropriate among patients ≥65 and treatment should be left to the discretion of the treating oncologist.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td><u>ALTA 201 phase 2 trial:</u>
The trial limited eligibility to patients with adequate organ and hematologic function.
<u>101 phase ½ trial:</u></td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results</td><td>The use of brigatinib should be limited to patients with adequate hematologic, hepatic and renal</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>The trial required that patient had adequate renal and hepatic function.</td><td>with respect to the target population?</td><td>function as determined by the treating oncologist.</td></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td><u>ALTA 201 phase 2 trial:</u>
201 trial was a global trial with that enrolled patients from 18 countries: Australia, Austria, Belgium, Canada, Denmark, France, Germany, Hong Kong, Italy, Republic of Korea, Netherlands, Norway, Singapore, Spain, Sweden, Switzerland, United Kingdom, United States.
Sites included 15 in the United States, 1 in Canada, 38 in Europe, 6 in Australia, and 11 in Asia.
<u>101 phase ½ trial:</u>
The 101 trial was completed in the United States and Spain.</td><td>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?</td><td>The ALTA study included Canada therefore there is no reason to believe that the results would be different in the Canadian population of patients with locally advanced or metastatic ALK positive NSCLC.</td></tr>
<tr><td></td><td>Biomarkers</td><td><u>ALTA 201 phase 2 trial:</u>
201 trial enrolled patients who had histologically or cytologically confirmed locally advanced or metastatic NSCLC that was ALK-positive ascertained by a validated FISH test or other test (but tissue available for the Vysis® FISH test).
Arm B: in 12 patients out of 110 no central FISH test was performed or was negative.
<u>101 phase ½ trial:</u>
Expansion phase (cohort 2): history of ALK rearrangement by FISH test.</td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)?</td><td>Determination of ALK positivity in Canada is standard. It uses an IHC test to screen advanced non-squamous NSCLC followed by confirmatory FISH in many cases.</td></tr>
<tr><td>Intervention</td><td>Prior treatments</td><td><u>ALTA 201 phase 2 trial:</u>
201 included patients who received prior chemotherapy:<table><tr><th></th><th>Arm B, 180 mg once daily (with lead-in) (N=110)</th></tr><tr><td>Any prior chemotherapy, N (%)</td><td>81 (73.6)</td></tr></table></td><td>1) Are the results of the trial generalizable to patients who did not received prior chemotherapy?
2) Are the results of the trial generalizable to patients who have received another ALK inhibitor, such as alectinib instead of crizotinib in first-line?</td><td>1) The CGP feels that the results are generalizable to patients without prior chemotherapy as the presence of the target rather than prior treatments is most responsible for the efficacy of the therapy.
2) The CGP acknowledges that there is limited information regarding alectinib resistance patterns and the subsequent efficacy of brigatinib. Nonetheless, the CGP feels that sequential targeted therapy would be</td></tr>
</table>

Domain	Factor	Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial	Generalizability Question	CGP Assessment of Generalizability
		Prior platinum-based chemotherapy, N (%) 80 (72.7) 201 trial eligibly criteria was that patients had progressive disease while on crizotinib, as assessed by the investigator or treating physician. **101 phase ½ trial:** Patients had received prior chemotherapy and crizotinib.		appropriate and the options would need to be re-evaluated over time as more data become available.
	Crizotinib intolerance	**ALTA 201 phase 2 trial:** According to the submitter the ALTA trial included crizotinib intolerance based on the investigators' clinical judgement, however, no data was captured on these patients. **101 phase ½ trial:** In study 101, patients (25/137) had been previously treated with crizotinib and received brigatinib, aligned with the current Health Canada approved dosing regimen. Out of 25 patients, only one patients was reported to have stopped crizotinib due to intolerance (with hepatic toxicity).	Are the results of the trial generalizable to patients who are intolerant to crizotinib? PAG also noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after one dose.	The ALTA trial did not report the number of patients who were intolerant to crizotinib. In the case of crizotinib intolerance, the CGP agreed that brigatinib may be a reasonable treatment alternative. The CGP felt that the definition of intolerance is side effects despite optimal medical management, as determined by the treating oncologist. The CGP also felt that it is very unlikely that crizotinib would be discontinued after one dose due to intolerance and likely the determination would be made after at least a cycle of therapy (28 days).
	Treatment intent	What was the intent of the treatment in the trials?	Are the results of the treatment generalizable to an alternative treatment intent?	The intent of treatment is palliative.
	Administration of intervention	**ALTA 201 phase 2 trial:** Patients were assigned brigatinib at a dose of 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (arm B). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Product Monograph recommends a dose of 180 mg once daily with a 7-day lead-in at 90mg. **101 phase ½ trial:**	Is the intervention administered differently (e.g., dose or schedule) in clinical practice than in the trial?	The dose and schedule including lead-in phase are familiar to clinicians and considered standard. It was implemented for the uncommon event of pulmonary adverse events of early onset. It is appropriate to follow the trial protocol to deliver the therapy in the safest fashion possible.

Domain	Factor	Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial	Generalizability Question	CGP Assessment of Generalizability
		Patients were enrolled in the study in two phases (dose escalation and expansion phases). In Phase 1, dose escalation occurred according to a standard 3+3 design starting at 30 mg and increasing the increment until the maximum tolerated dose was identified. In the expansion phase, three dosing regimens were assessed: 90 mg, 180 mg and 180 mg with a 7-day lead-in at 90 mg. Assignment to dosing regimens was not randomized. 25 patients in the 101 trial (n = 137) met the pCODR requested reimbursement criteria at the recommended dose of 180 mg once daily with a 7-da7 lead-in at 90mg.		
	Treatment until disease progression	**ALTA 201 phase 2 trial:** Treatment continued in the ALTA trial until disease progression or intolerable toxicity. Disease progression was assessed per RECIST v1.1 at the investigator's discretion. Patients in either arm who experienced disease progression could continue to be treated at the same dose, if in the opinion of the treating investigator they continued to experience benefit. **101 phase ½ trial:** Patients continued treatment until disease progression or intolerable toxicity as determined by the investigator.	Is treatment until disease progression handled differently in Canadian clinical practice than in the ALTA trial?	In NSCLC with molecular aberrations and effective targeted agents, Canadian clinical practice is to treat until lack of clinical benefit (progressive, symptomatic disease). Therefore treatment until disease progress would be handled in clinical practice as it was in the trial.

Domain	Factor	Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial	Generalizability Question	CGP Assessment of Generalizability
Comparator	Standard of care	ALTA 201 phase 2 trial: No comparator arm was included in the trial. 101 phase ½ trial: No comparator arm was included in the trial. Currently funded treatments for patients who have progressed on or are intolerant to crizotinib are alectinib, ceritinib, or chemotherapy. In order to assess the comparative efficacy brigatinib with these comparators, the pCODR Methods Team reviewed submitter-provided indirect treatment comparisons. Refer to section 7 for more details.	Are the findings of the trial generalizable to patients who may receive alectinib, ceritinib, or chemotherapy instead brigatinib?	Due to the lack of randomized comparative data, there is no reliable estimate of the comparative efficacy of brigatinib to ALK inhibitors or chemotherapy. The CGP suggests that, patient values and preferences, co-morbidities, treatment toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. Refer to section 7 for the complete critical appraisals of the submitter-provided ITsC.
Outcomes	Appropriateness of primary and Secondary Outcomes	ALTA 201 phase 2 trial The 201 trial measured the following clinical outcomes: Primary outcome: Confirmed ORR* investigator assessed as per RECIST v1.1 Secondary outcomes: Disease control rate, time to/duration of response, PFS, OS, and time on treatment. Safety, quality of life instruments. 101 phase ½ trial: The 101 trial measured the following clinical outcomes Primary outcome: ORR investigator assessed as per RECIST v1.1 Secondary outcomes: Confirmed ORR* (per central IRC), PFS, Duration of response, Overall survival (OS), PFS in patients with active brain metastases), CNS response (IRC-assessed intracranial confirmed ORR. Safety and tolerability. Results for all outcome measures are not provided in the post-hoc analyses of the 25 patients that were ALK-positive NSCLC with prior crizotinib use and a dosing of 180 mg once daily with a 7-day lead-in at 90 mg.	Were the primary and secondary outcomes appropriate for the trial design?	Response rate is a reasonable primary outcome for this study and the critical outcomes including PFS and OS were secondary endpoints. It is difficult to use RR as a surrogate marker for OS however, the CGP feels that the RR reflects the ability of therapy to inhibit the target and consequently would be associated with benefit.

Domain	Factor	Evidence from ALTA 201 phase 2 trial & 101 phase ½ trial	Generalizability Question	CGP Assessment of Generalizability
Setting	Supportive medications, procedures, or care	<u>ALTA 201 phase 2 trial:</u> The most frequent concomitant medications were: analgesics, drugs for acid-related disorders, antibacterials and corticosteroids for systemic use, antithrombotic agents, and psycholeptics. <u>101 phase ½ trial:</u> The most frequent concomitant medications were: analgesics, vitamins, antibacterials for systemic use, antiemetics and antinauseants, drugs for acid-related disorders, anti-inflammatory and antirheumatic products, psycholeptics, mineral supplements, drugs for constipation, antithrombotic agents, and corticosteroids for systemic use	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	Overall, brigatinib was well tolerated by patients. The majority of AEs were low grade with low toxicity. The CGP agree that given the modest side effects of brigatinib the support medications, procedures and care given in the trials are generalizable to the majority of Canadian treatment centres.

ALK = Anaplastic lymphoma kinase; CNS = central nervous system; IRC = independent review committee; NSCLC = non-small cell lung cancer; ALK = ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RR = response rate
*Confirmed ORR: RECIST v1.1-defined responses were confirmed with an imaging assessment that occurred at least 4 weeks after the first response.

1.2.4 Interpretation

Burden of Illness and Need

The Canadian Cancer Society estimates that in 2018, there were 28,600 new cases of lung cancer in Canada. If one assumes that 85% are NSCLC, 47% of which present with advanced or metastatic disease, and 4% of those are ALK-positive, the CGP estimates that the number of new cases with advanced ALK-positive NSCLC in 2018 was approximately 460.[22] This is a small but significant population of lung cancer patients with an estimated median survival of over 4 years[23] due to the availability of targeted therapy resulting in a larger prevalent population. The clinical profile of patients with ALK aberrations includes younger age and never smoking status, consequently patients with ALK positive disease have limited competing mortality.
Current front-line therapies include crizotinib and alectinib. Crizotinib is funded across Canada and provincial funding for alectinib is anticipated in the second quarter of 2019 with Alberta, Saskatchewan, and British Columbia being the first provinces to fund it in the first-line. Currently it is also available through a manufacturer's patient assistance program. 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.

Alternatives for brigatinib for patients who have failed crizotinib include ceritinib and alectinib (the latter, if not given in the first line setting). Ceritinib has received pCODR approval 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 in second line is currently publicly funded in all provinces, except Nova Scotia, Newfoundland and Labrador, and Prince Edward Island. Alectinib was approved by pCODR as 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. It has received provincial funding in Saskatchewan and other provinces are expected to follow suite. Currently it is also available through a manufacturer's patient assistance program. For patients treated with crizotinib, the therapy of choice in the second line setting is alectinib due to the excellent toxicity profile compared to ceritinib. Currently, ceritinib and alectinib in second line are not publicly funded in the Atlantic Provinces and platinum doublet chemotherapy would be an appropriate second-line treatment option if ALK inhibitors are not available.

To date there have not been large trials evaluating treatment after alectinib in first-line or in the second/third line setting after crizotinib, ceritinib and/or alectinib in patients with ALK-positive disease and the CGP feels that brigatinib represents an important new treatment option in these settings.

Effectiveness

Brigatinib is a third generation ALK inhibitor. It was evaluated in a phase II trial (ALTA) in patients who have progressed on crizotinib. Patients received brigatinib either at 90 mg given orally once daily (Arm A; n = 112) or at 180 mg once daily (with a 7 day lead-in dosing of 90 mg) (Arm B; n = 110). Each arm was evaluated separately with no statistical comparisons made between the two arms of the study. The focus of this pCODR review was on Arm B, as the dosing regimen of Arm B is aligned with the pCODR requested reimbursement criteria as well as with the Health Canada approved dosing regimen. Therefore, the CGP will focus primarily on the efficacy and safety results for Arm B.

Investigator-assessed confirmed objective response rate (ORR) was the primary end point. Secondary endpoints included ORR centrally reviewed, CNS response, duration of response, PFS, OS, safety and QOL. Inclusion/exclusion criteria included performance status ≤ 2, documented progression on crizotinib, patients must not have received any prior ALK inhibitor other than crizotinib, no symptomatic or neurologically unstable CNS metastases and no history of pneumonitis. Any number of prior chemotherapy regimens were permitted. Overall 73.6% of patients in Arm B received prior chemotherapy and prior platinum-based chemotherapy was received by 72.7% of patients in Arm B.

The results of ALTA demonstrated investigator-assessed confirmed ORR was 54% (97.5% CI, 43% to 65%) in Arm B. Investigator-assessed median PFS was 12.9 months (95% CI, 11.1 to not reached) in Arm B. IRC–assessed intracranial ORR in patients with asymptomatic measurable brain metastases at baseline was 67% in arm B. Median duration of response was 13.8 months (95% CI, 9.3 to not reached) in arm B. The IRC-assessed median PFS was 15.6 months (11.0 to not reached) [1]. The 1-year OS probability was 80% (67% to 88%).

The CGP acknowledged that in order to assess the comparative efficacy and safety of brigatinib to alectinib, ceritinib and chemotherapy in patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib, the pCODR Methods Team reviewed a submitter-provided ITC using naïve comparisons, unanchored matched-adjusted indirect comparisons (MAICs), and network meta-analyses (NMAs). The unanchored MAICs found that brigatinib statistically significantly improved PFS compared to ceritinib, alectinib, and chemotherapy, but no difference was found with crizotinib retreatment. Brigatinib also statistically significantly improved OS compared with ceritinib and crizotinib retreatment, but results were inconsistent when compared with alectinib and chemotherapy. No difference was found when brigatinib was compared to ceritinib or chemotherapy for discontinuation due to adverse events, and inconsistent results were seen when compared with alectinib. Brigatinib was associated with a lower likelihood of Grade 3 or 4 adverse events compared to alectinib; no difference was found when comparing brigatinib to ceritinib, and inconsistent results were seen when compared to chemotherapy. The quality assessment performed by the pCODR Methods Team determined that no decisive conclusion can be drawn from the manufacturer-submitted ITCs for how the effectiveness of brigatinib compares with that of alectinib, ceritinib, or chemotherapy. The main limitations of the ITC included the use of unanchored MAICs. The unanchored MAICs assumed that absolute outcomes can be predicted from the covariates, accounting for all effect modifiers and prognostic factors. This assumption is mostly considered impossible to meet, leading to an unknown amount of bias in the unanchored estimate. Further, the use of unanchored MAICs as head-to-head studies in the NMAs is a serious limitation of the NMAs, along with the double-counting of patients on brigatinib resulting in falsely improved precision in the NMAs. The comparative efficacy and safety estimates obtained are likely biased due to these limitations, and it is not possible to quantify or identify the direction of the bias. The CGP agreed with the Methods Team and cautioned against drawing conclusions from the ITCs on the magnitude of effect of brigatinib compared with brigatinib, ceritinib, or chemotherapy, given the absence of more robust direct evidence from a randomized trial and lack of long term outcomes such as survival and safety. However, the CGP noted that it seemed likely that in clinical practice brigatinib would compare favorable to standard chemotherapy regimens in terms of ORR, duration of PFS and toxicity. Chemotherapy in this advanced disease setting is associated with toxicities that negatively impact quality of life including multiple clinic visits for administration of therapy. The CGP also noted that it is likely that brigatinib's toxicity profile is superior to that of ceritinib. Based on clinical experience ceritinib is associated with GI toxicities that would be largely avoided with the use of brigatinib. The CGP concluded that there is insufficient evidence to determine the comparative effectiveness of brigatinib compared

to alectinib or ceritinib and therefore patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection. Refer to section 7 for the complete critical appraisal of the submitter-provided ITCs.

Safety

Common treatment-emergent adverse events (TEAEs) were nausea (40%), diarrhea (38%), headache (27%), and cough (34%), and were mainly grades 1 to 2. The most common grade ≥ 3 TEAEs were hypertension (6%) pneumonia (5%), increased lipase (3%) and increased blood creatine phosphokinase (9%). A subset of pulmonary adverse events with early onset occurred in 14 of 219 treated patients (all grades, 6%; grade ≥ 3, 3%); none occurred after escalation to 180 mg in arm B. 50% of patients were successfully retreated with brigatinib. Patient-reported outcomes data collected in the ALTA trial suggest that the toxicities of brigatinib were not detrimental to quality of life.

Overall, the CGP agreed that brigatinib has a toxicity profile that is manageable by clinicians and consistent with the safety profile of common second line ALK-inhibitor regimens. Despite the clear limitations of the non-comparative study design, the CGP suggests that brigatinib has a favourable toxicity profile compared to chemotherapy and ceritinib. Chemotherapy in this advanced disease setting is associated with toxicities that negatively impact quality of life including multiple clinic visits for administration of therapy. Ceritinib is associated with GI toxicities that has resulted in less uptake by physicians when alternatives exist. These safety concerns are largely avoided when brigatinib is used.

With brigatinib in the second line setting, the main limitations of ALTA include the phase II design with the lack of a standard comparator arm with a subsequent generation ALK inhibitor or platinum-based chemotherapy. ALTA also used response rate as a primary endpoint which is less relevant in the current era in which multiple targeted therapies for ALK inhibition are available and the duration of disease control has become one of the main deciding factors in treatment selection; however, PFS was a secondary endpoint. In addition, the inclusion criteria for the ALTA trial did not mandate prior platinum-based chemotherapy unlike the ASCEND 5 ceritinib and the ALUR alectinib trials. 74% of patients in ALTA did receive prior chemotherapy, however, which suggests that comparisons are reasonable.

At the first data cut-off date, the median follow up for arm B of ALTA was 8.3 months and with short follow up the OS data was not mature. The CGP further noted that the application of various subsequent treatments after disease progression may influence long-term OS estimates.

Several questions have been raised regarding the applicability of these results to certain patient populations:

1. Alectinib for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC was recently reviewed at pCODR. PAG noted that alectinib will likely become the standard first-line treatment option and is seeking guidance on the use of brigatinib following first-line treatment with alectinib.
    a. The landscape of ALK inhibition is constantly evolving making it challenging for evidence to be generated for the population at hand. Crizotinib has been the first line treatment option since it was approved in 2015. With the recent data

from J- ALEX and global ALEX in 2017, the positive pCODR recommendation in 2018, provincial funding in BC, Alberta and Saskatchewan, and the availability of a manufacturer's patient assistance program, many patients are on first line alectinib. There is still a prevalent population of patients who have been treated with crizotinib that may be considered for brigatinib. The difficulty lies in the evidence base for brigatinib after alectinib. The resistance mutations identified after alectinib suggest that there may still be benefit for brigatinib in this setting. Clinical data consists of a multi-institutional small cohort (n=22) study in alectinib refractory patients.[24] In this retrospective study, 67% of patients had PR or SD with brigatinib and the median PFS was 4.4 months. The role of brigatinib after alectinib has yet to be defined. Nonetheless, the CGP feels that sequential targeted therapy would be appropriate and the options would need to be re-evaluated over time as more data become available.

2. If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis: Patients who received first-line crizotinib and are currently receiving other second-line treatments (e.g., ALK inhibitors of ceritinib or alectinib, immunotherapy or chemotherapy) and have not progressed.
    a. For patients who received first line crizotinib and second line ceritinib or alectinib and have not progressed, the preference may differ depending on the agent and patient tolerance. Patients on ceritinib may be preferentially switched without progression to brigatinib if the patient experiences significant GI toxicity, a well-documented side effect with ceritinib. As alectinib is well tolerated with excellent efficacy results the CGP does not anticipate that stable, responding patients will be transitioned to brigatinib.

3. PAG noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after one dose. If brigatinib is demonstrating better benefits than crizotinib, brigatinib would essentially replace crizotinib as first-line treatment. PAG also noted there is a phase III trial (ALTA-1L) comparing brigatinib and crizotinib in previously untreated ALK-positive NSCLC. Overall, there is a strong potential for indication creep with brigatinib into the first-line setting.
    a. The definition of crizotinib intolerance in clinical practice can be variable related both to the grade of toxicity and the impact on quality of life. Even grade 2 toxicities can potentially be a cause for discontinuation of therapy due to the impact on the patient. From the phase III clinical trials of crizotinib, in the first line trial rates of adverse events deemed by the investigator to be related to treatment that resulted in permanent discontinuation was 5%.[25] The all cause grade 3-4 toxicities in this study were 14% elevated aminotransferase levels, 2% vomiting, constipation, diarrhea, 1% edema, vision changes and headaches. Similarly, in the second line crizotinib study the discontinuation rates was 6% for toxicity and the all cause grade 3-4 toxicities were 16% elevated aminotransferase levels, 4% dyspnea, 2% constipation, fatigue, 1% nausea, vomiting and dizziness respectively.[26] In clinical practice, crizotinib intolerance would include all of these potential toxicities. From a practical perspective, use of brigatinib in this setting would be appropriate given its activity in the ALTA and ALTA-1L study. The CGP noted that it is very unlikely that crizotinib would be discontinued after one dose due to intolerance and likely the determination would be made after at least a cycle of therapy (28 days).

4. Brigatinib is an oral tablet with multiple strengths, dose adjustment is accomplished by adjusting the number of tablets to take. This is an enabler to implementation. However, PAG noted there may be a potential for drug wastage for dose adjustments from 180mg back to 90mg daily.
    a. The ALTA study (arm B) included only 8% of patients with ECOG performance status of 2. In clinical practice dose reductions are much more common given that in the real world patients often have other comorbidities and functional limitations than trial patients. The CGP felt that dose reduction may be as high as 40% when implemented in practice.

       In their feedback to the initial recommendation, the submitter noted that brigatinib's oral route of administration, convenient once-daily dosing (compared to 8 times/day for alectinib and 5 times/day for ceritinib) and blister packaging is an enabler of adoption feasibility. PAG specifically noted that oral administration is an enabler to implementation. In response to the submitter's feedback, the pCODR Clinical Guidance Panel (CGP) suggested that patient compliance is likely better with once daily dosing as patients may forget to take their tablets when doing well. However, the CGP noted that this consideration would only be important if the clinical benefit among ALK inhibitors is similar which has not been established yet.

5. PAG is seeking clarity on treatment until "disease progression", treatment duration and treatment discontinuation.
    a. In NSCLC with molecular aberrations and effective targeted agents, clinical practice is to treat until lack of clinical benefit. This practice developed because in the Epidermal Growth Factor Receptor (EGFR) population it was noted that when patients were discontinued from the EGFR tyrosine kinase inhibitor (TKI) without implementation of another therapy there was disease flare.[28] The previously suppressed malignant cells grew rapidly with the development of significant symptoms, deterioration of quality of life and subsequently death, once the suppressive EGFR TKI was removed. As a result of this clinical phenomenon the practice has been to treat until lack of clinical benefit with targeted therapies including ALK inhibitors. With the 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. A lack of clinical benefit would be consistent with progressive, symptomatic disease.

6. As brigatinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation. Additional pharmacy resources will be required for drug preparation, administration time, and monitoring for multiple severe adverse effects including pulmonary toxicity (i.e., interstitial lung disease) and drug-drug interactions. PAG also noted some patients may require emergency treatment for interstitial lung disease.
    a. The development of pulmonary adverse events with early onset with brigatinib occurred in 6% all grades and 3% grade $\geq$3 in ALTA and 4%/3% in ALTA-1L respectively. Predictors for this toxicity included older age and shorter interval (<7 days) between the last dose of crizotinib and first dose of brigatinib. Management included steroids but a small subset of patients who experience this toxicity required oxygen supplementation. The pulmonary toxicity was a

self-limited pneumonitis like event. There is a heightened awareness of this toxicity in the lung oncology community with the recommendation to start treatment early in the week as the median time to onset was 2 days. Patients should be monitored for new or worsening respiratory symptoms particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, brigatinib should be held and the patient evaluated for other causes of symptoms.

In the first line ASCEND 4 and second line ASCEND 5 trial, 2% and less than 1% of patients developed grade ≥ 3 interstitial pneumonitis that was suspected to be related to ceritinib.[29,30] In the alectinib trials, the Japanese group reported grade ≥ 3 interstitial pneumonitis in 5% versus the global first line study 0% and ALUR did not note this as a significant toxicity.[1,31,32] The rates of pulmonary toxicities in the ceritinib and alectinib trials were for the duration of therapy in contrast to brigatinib where the focus was immediately after initiation of treatment. In assessing pulmonary toxicity, it is recognized to be an uncommon but consistent toxicity across the class of ALK inhibitors and brigatinib does not represent side effects out of keeping with the comparator agents.

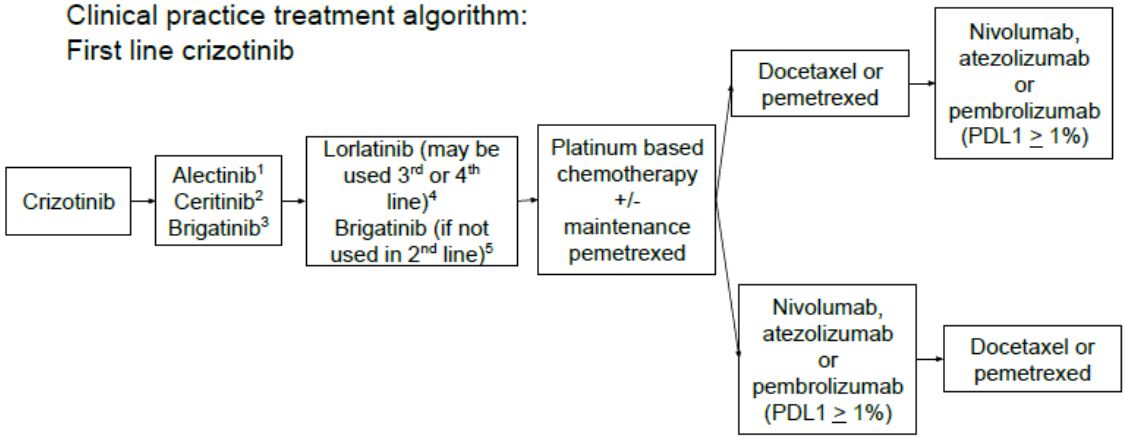
Sequencing questions:

7. Please consider the optimal sequencing of treatments for patients with ALK-positive NSCLC, specifically: ALK inhibitors (crizotinib, alectinib, ceritinib), chemotherapy, and immunotherapy. In clinical practice, if brigatinib was available:
    a. What would your preference be for second-line ALK inhibitor (i.e., brigatinib, alectinib, or ceritinib) following crizotinib? Please comment on the preference considering patient preference, efficacy, safety, and administration.
        i. Based on efficacy and toxicity profiles all three agents; alectinib, brigatinib and ceritinib are reasonable options in the second line setting with a preference in clinical practice for the former two due to superior tolerability.

    b. Is there preference as well as evidence to support sequencing of second-generation ALK inhibitors (e.g., alectinib or ceritinib followed by brigatinib) in patients who have progressed on or who were intolerant to crizotinib?

In response to Q. 7a and 7b, the CGP include the following Figure 1.1:

Figure 1.1: CGP suggested treatment algorithm- first-line crizotinib



Clinician preference is to treat with as many targeted options as possible prior to considering standard chemotherapy. The later generation ALK inhibitors have similar activity against ALK resistance mutations. Some clinicians may consider only 3 or attempt 4 lines of targeted treatment depending on availability and molecular profiling.

1. ALUR.
2. ALTA.
3. ASCEND 5
4. Solomon et al. Lorlatinib in patients with *ALK*-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Onc 19:12;1654-1667, Dec 2018. Lorlatinib is available through a special access program offered by Pfizer. The study demonstrated activity of lorlatinib in an ALK positive population in which 47% had 2 or more ALK inhibitors; RR 39% and PFS 5.5 m.
5. Due to the availability of alectinib in the second line setting through a patient assistance program, there will be a prevalence population of patients who have received 2 ALK inhibitors and may be considered for subsequent therapy. While there is no available evidence to support brigatinib in the 3rd line setting, many clinicians may consider this treatment option followed by lorlatinib. Brigatinib is available through a patient assistance program.

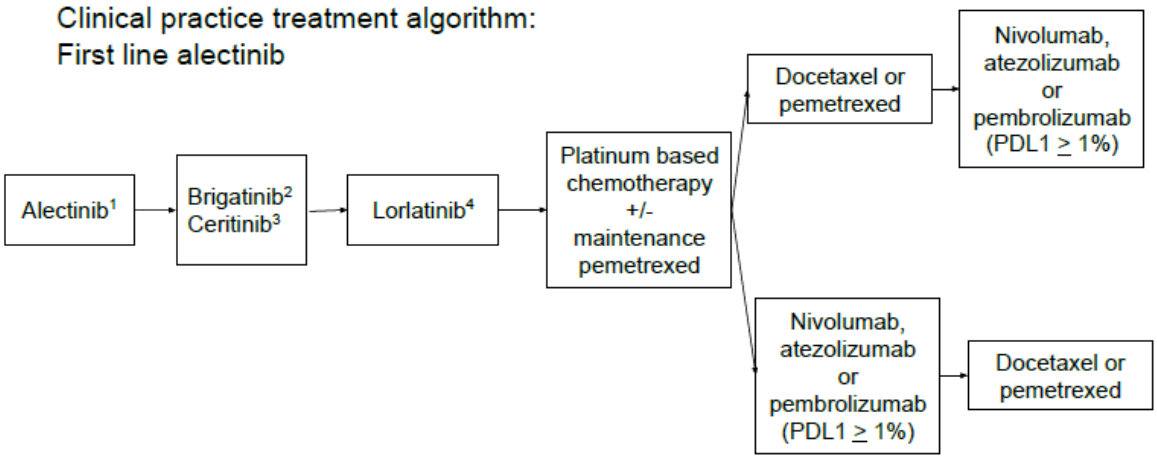
8. In jurisdictions where there is no publically funded ALK inhibitor in the second-line setting, would brigatinib in the third-line setting following chemotherapy be considered?
    a. The use of brigatinib after first line ALK inhibitor and platinum-based chemotherapy would be reasonable. In ALTA 74% of patients received chemotherapy prior to enrollment which supports the efficacy of brigatinib after conventional chemotherapy.

9. PAG noted clinicians may prefer to use available ALK inhibitors sequentially rather than alternatively. PAG is seeking clarity on the use of brigatinib in later lines of therapy, for example, as third-line treatment following second-line ceritinib and first-line crizotinib.
    a. Although there is little data regarding the activity of brigatinib in patients previously treated with alectinib alone or both crizotinib and ceritinib or crizotinib and alectinib, the CGP feels it would be reasonable to offer brigatinib to patients intolerant of or progressing after alectinib alone or both crizotinib and ceritinib or crizotinib and alectinib. This recommendation is on the basis of emerging data regarding ALK resistance mutations with ceritinib or alectinib that may remain sensitive to brigatinib.[33] Clinical data consists of a multi-institutional small cohort (n=22) study in alectinib refractory patients.[24] In this retrospective study, 67% of patients had PR or SD with brigatinib and the median PFS was 4.4 months. The role of brigatinib after alectinib has yet to be defined.

10. PAG is also seeking guidance for patients who do not tolerate second-line ceritinib and whether switching to brigatinib would be appropriate. Similarly, for patients who do not tolerate brigatinib, whether it would be appropriate for these patients to switch to ceritinib.
    a. Intolerance to any alternate ALK inhibitor in the second line setting (ceritinib 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.

11. Please comment on the number of ALK inhibitors a patient should receive in their treatment trajectory for ALK-positive NSCLC.
    a. To date there is evidence for two lines of ALK inhibition to manage disease. In clinical practice, physicians may opt to consider 3-4 agents depending on reimbursement from public and private sources as well as patient assistance or special access programs. In the setting of a druggable mutation, clinician preference is to exhaust all targeted options before moving to chemotherapy.

Figure 1.2: CGP suggested treatment algorithm- first-line alectinib



Clinician preference is to treat with as many targeted options as possible prior to considering standard chemotherapy. The later generation ALK inhibitors have similar activity against ALK resistance mutations.

1. J ALEX, ALEX
2. ALTA. Note is made that this study was in a post-crizotinib population and an extrapolation of the results to the alectinib population.
3. Hida T, et al. Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma kinase-rearranged metastatic non-small-cell lung cancer in Japan: ASCEND-9. Cancer Sci. 2018 Sep;109(9):2863-2872
4. Solomon et al. Lorlatinib in patients with *ALK*-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Onc 19:12;1654-1667, Dec 2018. Lorlatinib is available through a special access program offered by Pfizer. The study demonstrated activity of lorlatinib in an ALK positive population in which 47% had 2 or more ALK inhibitors; RR 39% and PFS 5.5 m.

1.3 Conclusions

Brigatinib versus chemotherapy

The CGP concluded that there is a net clinical benefit to brigatinib, compared with chemotherapy, in the treatment of adult patients with ALK-positive locally advanced or metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib). This conclusion is based on the results achieved in Arm B (n = 110) of the non-comparative ALTA trial which showed a high response rate and encouraging PFS, with a clinically acceptable toxicity profile that does not worsen health related quality of life and appears to be better than that experienced with chemotherapy (single-agent or platinum-based doublet chemotherapy). These data suggest much greater clinical benefit than what would be expected from standard chemotherapy regimens in this setting. Responses in this patient population are important because of the accompanying improvement in distressing disease symptoms (extreme fatigue, weakness, breathing difficulties, cough, and pain) and improvement in performance status. Brain metastases occur frequently in patients with *ALK-positive* NSCLC and have the potential to significantly impact patients' quality of life. Exploratory analyses from the ALTA trial suggest that patients with asymptomatic measurable baseline CNS metastases may have good response with brigatinib. Given that current standard of care options after crizotinib have a median PFS of less than 1 year, more effective therapies which improve survival rates with activity against a broader spectrum of mutations and CNS penetration are urgently required in this population.

Brigatinib versus alectinib or ceritinib

The CGP concluded that there may be a net clinical benefit to brigatinib, compared with alectinib or ceritinib, in the treatment of adult patients with ALK-positive locally advanced or metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib). This conclusion is based on the results achieved in Arm B (n = 110) of the non-comparative ALTA trial which showed a high response rate and encouraging PFS. The secondary endpoint of PFS demonstrated a prolonged response to therapy which appeared to be longer than the PFS with alectinib or ceritinib. However, the CGP noted that the magnitude of effect compared with alectinib and ceritinib is uncertain given the lack of comparative data and long-term outcomes such as survival and safety. The CGP acknowledged that brigatinib showed a manageable toxicity profile but was unable to determine how it compares with the safety profile of alectinib, which is generally well tolerated. Based on clinical experience the CGP and the registered clinicians providing input agreed that brigatinib's toxicity profile appears to be better than that experienced with ceritinib. However, the CGP agreed that more robust direct evidence from a randomized trial is required to address the comparative effectiveness and safety of brigatinib compared to alectinib and ceritinib in this setting. The Indirect treatment comparisons provided by the submitter have a substantial risk of bias and no firm conclusions can be drawn from these comparative effect and safety estimates.

Given the paucity of data regarding the benefits of one ALK inhibitor over another in the second line setting the CGP suggested that all three agents; alectinib, brigatinib and ceritinib, remain reasonable options for therapy and other factors including toxicity, resistance mechanism, and molecular characterization may provide a rationale for a specific choice.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The recommendation is made on the basis of a non-comparative, single therapeutic option study, however, it is further supported by the phase III data provided by the ALTA-1L study

comparing brigatinib and crizotinib.

- The presence of pulmonary adverse events with early onset does set brigatinib apart from its comparators, however, the incidence is low and not out of keeping with pneumonitis rates seen through the course of treatment with crizotinib, ceritinib and alectinib.

- The landscape of ALK inhibition is constantly evolving making it challenge for evidence to be generated for the population at hand. Consequently, other sources of information including resistance patterns and real world data will need to be considered to provide guidance for data gaps. The CGP recommends consideration of brigatinib after alectinib first line despite the absence of clinical trials data to allow patients the options of a minimum of 2 lines of targeted therapy.

- The CGP noted that the majority of patients included in the brigatinib trial (ALTA) had received platinum-based chemotherapy in addition to crizotinib. The CGP agreed, that the results of the ALTA trial are generalizable to patients without prior chemotherapy as the presence of the target (the ALK tyrosine kinase receptor enzyme) rather than prior treatments is most responsible for the efficacy of the therapy.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada. Non-small cell lung cancers (NSCLC) are the most common type of lung cancers, comprising 85% of lung cancers. In 2018, it is estimated that there will be 28,600 new cases of lung cancer diagnosed and 21,100 deaths associated with lung cancer.[34] NSCLC represents approximately 85 % of all cases of lung cancer and for the purposes of therapeutic decision, are categorized by histologic appearance as either squamous or non-squamous NSCLC. The majority of patients with NSCLC will present with or develop advanced/metastatic disease. For these patients, treatment intent is to palliate symptoms and prolong survival.

In patients with non-squamous NSCLC, the first step in determining treatment options is assessment of molecular markers, including chromosomal rearrangement of the Anaplastic Lymphoma Kinase (ALK) gene on chromosome 2 (ALK+ 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+ NSCLC, including younger age at diagnosis, never smoking status and adenocarcinoma histology.[35] Although no national data is available for Canadian patients, The French Cooperative Thoracic Intergroup (IFCT) report a 5% ALK positivity in 8134 patients assessed in the 1 year period between April 2012-April 2013.[36] Central nervous system (CNS) metastases are quite common in ALK+ 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.[37]

2.2 Accepted Clinical Practice

First-line

There are three agents with phase III trials in first line ALK positive NSCLC; crizotinib, ceritinib and alectinib. Both crizotinib and alectinib are pCODR approved. Crizotinib is funded in many provinces and provincial funding for alectinib is anticipated in the second quarter 2019 with Alberta and Saskatchewan already funding it in the first-line. Crizotinib, an oral small molecule inhibitor of ALK, MET and ROS1 kinase, was the first approved therapy for first-line therapy for metastatic ALK+ NSCLC in Canada. This is based on an open label phase III study that confirmed superior objective response rates [74% vs. 45%, (P<0.001)] and progression-free survival (PFS) [median 10.9 months vs. 7.0 months; hazard ratio (HR) for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001)] favouring crizotinib when compared to first-line platinum doublet chemotherapy; overall survival was not different between the two arms, likely due to the high rate of cross-over to crizotinib in the chemotherapy arm.[25] 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. In addition, the CNS appears to be a common site of progression on crizotinib, likely related to the low penetration of crizotinib into the CNS. If 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.

The second generation ALK inhibitor, ceritinib, also has activity in the first line setting. ASCEND 4 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+ treatment naïve patients.[29] 376 patients were randomly assigned to ceritinib (n=189) and chemotherapy (n=187). The primary endpoint was blinded independent review committee (BIRC) assessed PFS; 16·6 months (95% CI 12·6–27·2) in the ceritinib group and 8·1 months (5·8–11·1) in the chemotherapy group (HR 0·55 [95% CI 0·42–0·73]; p<0·00001).[29] Ceritinib is Health Canada approved in the first line setting but has not been submitted to pCODR for consideration and consequently is not standardly used in Canada.

Alectinib is a second generation ALK inhibitor that was evaluated in the first line setting against crizotinib in two phase III trials; J ALEX[31] and Global ALEX.[32] 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. 207 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 not yet been reached with alectinib and was 10·2 months (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[32] 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. 152 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 m in the alectinib group and was 10.8 months in the crizotinib group (stratified HR 0.43, 95% CI 0.32–0.58).[23] 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 pCODR for the treatment of patients with ALK+, 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.

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.[38] Off target mechanisms of resistance include upregulation of other signalling pathways. Molecular characterization of crizotinib resistant patients identified a resistance mutation in 20%; L1196M (7%) and 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.[33] 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 in considering second line therapy as different agents have different capabilities of addressing these ALK fusion protein changes.

Second line

Certinib has demonstrated ability to overcome resistance to crizotinib in the second line setting. ASCEND 5[30] was a phase III RCT that assessed the efficacy and safety of ceritinib in patients with locally advanced or metastatic ALK+ 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 arm were treated with either docetaxel or pemetrexed, investigator's choice. Patients with documented disease progression in the ceritinib arm 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 arm 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+ NSCLC ((5·4 months vs 1·6 months, HR 0.49; 95% CI, 0.36 to 0.67, p<0.001). The response rate was superior with ceritinib 45% vs chemotherapy 7%. OS 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 to 1.49, p=0.496). Ceritinib has received pCODR approval in March 2017 for treatment as monotherapy in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib. Ceritinib in second line is currently publicly funded in most of the provinces.

Alectinib also demonstrates activity in the second line setting with the phase III trial, ALUR,[39] 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. 107 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% confidence interval (CI): 6.9-12.2] with alectinib and 1.4 months (95% CI: 1.3-1.6) with chemotherapy [hazard ratio (HR) 0.15 (95% CI: 0.08-0.29); P < 0.001]. Independent Review Committee (IRC)-assessed PFS was also significantly longer with alectinib [HR 0.32 (95% CI: 0.17-0.59)]. Investigator-assessed ORR was 37.5% 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 approve by pCODR as monotherapy for the treatment of patients with ALK+, 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, the therapy of choice in the second line setting is alectinib due to the excellent toxicity profile compared to ceritinib and it is currently available through a manufacturer's patient assistance program.

To date there have not been large trials evaluating treatment after alectinib in first line or in the second/third line setting after crizotinib, ceritinib and/or alectinib in ALK+ patients. For patients in this setting, platinum doublet chemotherapy, particularly platinum combined with pemetrexed is an additional option for treatment. Currently, ceritinib or alectinib in second line are not publicly funded in the Atlantic Provinces and platinum doublet chemotherapy would be an appropriate second-line treatment option if ALK inhibitors are not available. Platinum pemetrexed chemotherapy appears to have activity in ALK positive NSCLC that is similar to that seen in advanced NSCLC without ALK rearrangements.[40]

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[41] included patients

with driver mutations and evaluated bevacizumab, carboplatin, and paclitaxel plus or minus atezolizumab as first line chemotherapy treatment however, only 37 ALK+ patients were included. In the second line setting CHECKMATE 057, KEYNOTE 010 and OAK evaluated single agent immunotherapy versus chemotherapy but only accrued a small number of ALK+ patients 21, 8 and 2 respectively.[42-44] 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 however, this does not appear to correlate with clinical benefit.

Brigatinib is seeking reimbursement approval for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK inhibitor (crizotinib). The request has been made in the changing landscape of ALK+ management where there is currently a transition from crizotinib to alectinib first line where it is acknowledged that the resistance pattern may be different and drug sensitivities are not as predictable.

2.3 Evidence-Based Considerations for a Funding Population

The Canadian Cancer Society estimates that in 2018, there were 28,600 new cases of lung cancer in Canada.[34] If one assumes that 85% are NSCLC, 47% of which present with advanced / metastatic disease, and 4% of those are ALK-positive, the CGP estimates that the number of advanced ALK-positive NSCLC in Canada in 2018 was approximately 460.[22] Determination of ALK positivity in Canada is standard. It uses an immunohistochemistry test to screen advanced non-squamous NSCLC, with confirmation in equivocal cases by fluorescent in-situ hybridization.[45] Testing would have been done in the population under consideration in order for them to have received crizotinib or alectinib as initial ALK-directed therapy. Currently, testing for resistance mutations in ALK+ NSCLC is not incorporated into clinical practice as there was no clinical decision to be made with the information.

Brigatinib is a third generation ALK inhibitor. It was evaluated in a phase II trial (ALTA)[1] after crizotinib failure comparing 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (arm B). Investigator-assessed confirmed objective response rate (ORR) was the primary end point. Inclusion/exclusion criteria included performance status $\leq$ 2, patients must not have received any prior ALK inhibitor other than crizotinib and no symptomatic neurologically unstable CNS metastases. Patients were not required to have prior platinum-based chemotherapy, unlike ASCEND 5 and ALUR. 222 patients enrolled and 69% had baseline brain metastases and 74% had received prior chemotherapy (type not specified). The investigator-assessed confirmed ORR was 45% (97.5% CI, 34% to 56%) in arm A and 54% (97.5% CI, 43% to 65%) in arm B. Investigator-assessed median PFS was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months (95% CI, 11.1 to not reached) in arms A and B, respectively. IRC–assessed intracranial ORR in patients with measurable brain metastases at baseline was 42% in arm A and 67% in arm B. Common treatment-emergent adverse events were nausea (arm A/B, 33%/40%), diarrhea (arm A/B, 19%/38%), headache (arm A/B, 28%/27%), and cough (arm A/B, 18%/34%), and were mainly grades 1 to 2. A subset of pulmonary adverse events with early onset occurred in 14 of 219 treated patients (all grades, 6%; grade $\geq$ 3, 3%); none occurred after escalation to 180 mg in arm B. 50% of patients were successfully retreated with brigatinib. In the second line setting, brigatinib outcomes parallel alectinib and are numerically superior to ceritinib.

There is further evidence to support the efficacy of brigatinib in this subgroup of NSCLC patients. In ALTA 1L,[46] 275 ALK inhibitor naïve patients were randomized to brigatinib at a dose of 180 mg once daily (with a 7-day lead-in period at 90 mg) or crizotinib at a dose of 250 mg twice daily. The primary endpoint was positive as the PFS was higher with brigatinib than with crizotinib (estimated 12-month PFS 67% [95%CI, 56 to 75] vs. 43% [95% CI, 32 to 53] and HR 0.49

[95% CI, 0.33 to 0.74]; P<0.001 by the log-rank test). The confirmed objective RR was 71% (95% CI, 62 to 78) with brigatinib and 60% (95% CI, 51 to 68) with crizotinib; the confirmed rate of intracranial response among patients with measurable lesions was 78% (95% CI, 52 to 94) and 29% (95% CI, 11 to 52), respectively.

The characterization of resistance mutations associated with ALK inhibitor treatment and cell line work suggest that brigatinib may be effective against resistance mutations that are not addressed by ceritinib or alectinib. It is unclear whether the preclinical work will reflect the clinical experience with these therapies.

It is difficult to estimate the potential number of patients in Canada for whom brigatinib after progression on crizotinib would be the recommended treatment. While it may be simple enough to use crude incidence rates for advanced NSCLC and the expected percentage of ALK positive patients to arrive at an estimate, these crude calculations likely over-estimate the number of eligible patients. It is clear that not all patients with advanced NSCLC have molecular testing done, either because of lack of accessible/adequate tissue samples or because they are too ill for systemic therapy (poor PS or co-morbidities) or because of death on treatment. It is also clear that not all patients receiving crizotinib will receive subsequent therapy, due to decline in PS or unresolved toxicities. The availability of brigatinib for patients progressing on crizotinib may alter patterns of practice in that fewer patients may be treated beyond progression with crizotinib and be switched to brigatinib. In addition, with the availability of alectinib through patient assistance programs, there will be a population of ALK-positive patients that have never been treated with crizotinib.

2.4 Other Patient Populations in Whom the Drug May Be Used

The funding indication being sought is in patients with ALK-positive NSCLC intolerant to crizotinib or with progression following crizotinib. It is likely that the number of patients who will receive alectinib as first line therapy will increase due to the results of the J ALEX and Global ALEX trial. Although there is little data regarding the activity of brigatinib in patients previously treated with alectinib alone or both crizotinib and ceritinib/alectinib, the CGP feels it would be reasonable to offer brigatinib to patients intolerant of or progressing after alectinib alone or both crizotinib and ceritinib/alectinib. This recommendation is on the basis of emerging data regarding ALK resistance mutations with ceritinib/alectinib that may remain sensitive to brigatinib.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input on brigatinib for the treatment of adult patients with anaplastic lymphoma kinase positive (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

LCC used two sources of information for its submission. The LCC conducted a 15-minute national online survey, the Faces of Lung Cancer Report (FOLCR) survey, from August 12th, 2015 to September 1st, 2015. This survey included 91 former or current patients with lung cancer, and 72 former or current caregivers of patients with lung cancer, who were ≥ 18 years of age. Of the patient respondents, 57% did not currently have lung cancer. Of the caregivers, 79% formerly provided care for a patient with lung cancer; with 68% reporting care was stopped due to the patient passing away and 32% reporting the patient recovered. Of the 163 completed surveys, 162 were Canadian respondents, and 1 was a respondent from the US. Additionally, an environmental scan was conducted of online forums to collect data specific to the present pCODR submission. Data on patients' and/ caregivers' views regarding previous and current treatments as well as their needs were accessed between November and December 2018, which included 7 patients with lung cancer and 4 caregivers. Of the 11 patients and caregivers, 7 were male (64%) and 4 (36%) were female. The age range for this group was 15 to 70 years of age. Please see details on demographic data related to the environmental scan below (Table 3.1).

Table 3.1: Summary of patient and caregiver demographics access through the environmental scan conducted by LCC

Input Source	Gender	Age	Caregiver/Patient
Environ Scan	Male	58	Patient
Environ Scan	Male	40	Patient
Environ Scan	Female	N/A	Caregiver
Environ Scan	Male	N/A	Caregiver
Environ Scan	Female	65	Patient
Environ Scan	Male	N/A	Caregiver
Environ Scan	Male	70	Patient
Environ Scan	Male	N/A	Patient
Environ Scan	Female	46	Patient
Environ Scan	Male	15	Caregiver
Environ Scan	Female	60	Patient

OLA conducted a phone interview with one patient with lung cancer in November 2018, and received input from 91 online surveys completed by people living with a chronic lung condition and/or their caregivers in December 2018. Of these 91 surveys, four were completed by patients with lung cancer (2 female, 2 male). Feedback from a certified respiratory educator was also included. All information was obtained from Canadian respondents.

From the patient's perspective, the impact of a lung cancer diagnosis can leave patients completely shattered and overwhelmed causing them to worry about available treatment options, survival and their loved ones. LCC noted that for patients with ALK-positive disease, just knowing there is treatment targeted to their mutation gives them hope and the ability to face each day with positivity. OLA reported that some of the symptoms related to lung cancer include extreme fatigue and exhaustion, weakness, breathing difficulties (such as shortness of breath), cough, and pain. Symptoms change frequently, which impacts daily activities, day-to-day planning, and can be challenging to manage. OLA also highlighted that lung cancer negatively impacts patients' relationships with family and friends, independence, emotional well-being, and financial situation, resulting in a significant emotional toll followed by depression. In addition, OLA noted that several patients stated the need for clearer communication and information regarding their disease and available treatment options in order to cope with their condition and to plan out next steps.

Current therapies for 2nd line treatment after progression on crizotinib include chemotherapy or chemoradiation, ceritinib, and alectinib. As reported by the LCC, chemotherapy has many side effects that interfere with daily activities as well as require multiple, and often quite long, hospital visits for intravenous infusions. Though not all patients will experience toxicities, the prospect of going on chemotherapy is devastating to patients. Patients receiving treatment with ceritinib on the other hand described the experience as a continuation of hope, with patients being able to maintain a high level of functioning and active lives. Side effects were reported to be manageable, and many patients achieved control of their cancer, including brain metastases. Patients that received alectinib also saw a reduction in tumor size and lung cancer symptoms. Given that ceritinib and alectinib are oral treatments, patients and their caregivers were not burdened or inconvenienced with long hospital visits or recuperation time.

In terms of expectations for alternative treatment options LCC noted that focus was placed on manageable side effects and extension of life and quality of life. More specifically patients' expectations included: the ability to maintain a high level of functionality, to continue to parent, to work, to maintain family life, and to enjoy life (e.g., travel and go on vacation). LCC also highlighted the importance of new and better treatments that provide the opportunity to extend survival, give patients hope for the future, and provide time to wait for new treatment options. OLA reported that overall patients desire treatments that will increase independence, require less assistance from others, and improve energy. More specifically patients' expectations included: stopping or slowing the disease progression, reducing side effects, maintaining quality of life, administering of treatments at home, and having less or no cost burden associate with the new treatment.

LCC provided the perspective of 5 patients and 4 caregivers with experience with brigatinib. According to LCC three key themes emerged from the patient experience with brigatinib: (i) it was effective in controlling cancer (including brain metastases), (ii) it had manageable side effects, and (iii) it allowed patients to have a good quality of life. In particular patients reported that brigatinib led to stable disease, reduced or eliminated brain metastases, overcame disease resistance to crizotinib and allowed continuation of an active life style. Common side effects of brigatinib included fatigue, vomiting, diarrhea, constipation, abdominal pain, and muscle and joint paint. A few patients indicated that, compared with crizotinib, they had tolerated brigatinib better with fewer side effects. LCC indicated that patients were able to continue an active life style while receiving brigatinib.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Lung Cancer

LCC reported that NSCLC is the most common type of lung cancer occurring in 80-85% of cases, with many cases being diagnosed at an advanced and non-operable stage. In Canada, NSCLC accounts for 26% of all cancer deaths and the five year survival rate is just 17%, with even lower rates for advanced cases. LCC highlighted that when a patient is given a diagnosis of advanced lung cancer, it can leave them completely shattered and overwhelmed causing them to worry about available treatment options, survival and their loved ones. For patients with ALK-positive disease, just knowing there is treatment specifically targeted to their mutation gives them hope and the ability to face each day with positivity. LCC noted that the ALK mutation is found in about 3-5% of patients with lung cancer and current molecular driven therapies allowed patients to live longer and have a better quality of life. According to LCC treatments such as alectinib and crizotinib have been approved in the first line for ALK-positive mutations. However, due to the possibility of disease progression or intolerance to first line treatments, it is necessary to provide second line options to reduce the risk of tumor spread and CNS involvement as well as possible death. LCC noted that brigatinib, a targeted cancer therapy which acts as an ALK inhibitor, is a second line form of treatment for the treatment of ALK-positive NSCLC which has been approved by the FDA and has the potential to prolong survival and improve patient outcomes.

LCC provided the following details about a patient who was diagnose with stage 4 NSCLC:

The patient was given six months to two years to live. LCC reported the following quote from this patient: "*to say this was quite the shock was an understatement*". LCC reported further that the patient was a very active person who hiked (the Appalachian Trail), biked and swam regularly. Six years later, after seven different chemotherapy sessions, and a four and a halve year run on crizotinib, which provided incredible results and a better quality of life, the patient subsequently developed brain metastases. The patient was then put on brigatinib, and is currently on the fifth cycle and is experiencing an even better quality of life.

OLA mentioned that patients feel frustrated with the length of time and number of appointments it takes for patients to receive an accurate diagnosis, with one female patient reporting, "*It took close to a year, with many appointments and referrals to finally get to the right specialist and receive a proper diagnosis and learn about my prognosis*". A daughter of a patient with lung cancer stated, "*The most frustrating thing for me was how long it took to get her diagnosed.*" OLA also mentioned that respondents did not have sufficient information to understand their disease (both cancer in general and lung cancer specifically), treatment options, and eventual prognosis. Respondents expressed a need for adequate information in order to make decisions about next steps. Several respondents mentioned they felt rushed at appointments with doctors, and they would like to receive information in "*easy to understand*" language with a clear picture of their treatment options.

OLA reported that patients experienced extreme fatigue and exhaustion, which was difficult to handle and required patients to plan their days around managing exhaustion. Additional symptoms and problems experienced by patients included pain, which could be intense at times, shortness of breath, cough, and weakness. One patient described their experience with these symptoms as, "*I need supplemental oxygen for every action, and I suffer from terrifying breathless episodes*". Symptoms were reported to be inconsistent, to change frequently, and to be therefore difficult to manage. The OLA emphasized the impact lung cancer has on day-to-day life, such as its impact on the ability to work, travel,

socialize, and participate in leisure and physical activities. OLA also highlighted the impact on patients' relationships with family and friends, independence, emotional well-being, and financial situation. One patient was quoted as saying: "*My movement is restricted and I am short of breath and tired all of the time. This disease has affected all parts of my life. I am no longer able to swim or babysit my grandchildren and often feel alone and 'shut-in'. It is very hard to be positive and hopeful.*"

3.1.2 Patients' Experiences with Current Therapy for Lung Cancer

LCC indicated that currently, the standard second-line therapy for patients with ALK-positive NSCLC who have progressed on or who were intolerant to crizotinib is chemotherapy, ceritinib or alectinib. LCC noted that ceritinib is funded in some jurisdictions in Canada, while alectinib has recently been reviewed by pCODR. LCC noted that patient experiences with these forms of treatment have been well documented in previous submissions.

Regarding chemotherapy, LCC reported that patients experienced side effects that interfered with daily activities. While some patients experienced minimal symptoms, many reported side effects commonly associated with chemotherapy such as nausea, vomiting and extreme fatigue. Patients also reported the inconvenience of multiple hospital visits for the intravenous infusions of chemotherapy as well as the toxicities associated with the treatment. Chemotherapy also affected patients' ability to work, which could result in financial hardship for their families.

LCC concluded that for many patients the thought of going on chemotherapy would be devastating.

LCC also commented on chemoradiation, noting that it is known to lower patients immunity and in some cases has wiped out patients' white and red blood cells. This typically results in an inability to go out, return to work, have visitors and even spend quality time with family and loved once.

The LCC conveyed that patients' experience on ceritinib post-crizotinib allowed them to continue being hopeful. Patients felt great, experienced manageable side effects, and improved outcomes. Patients were highly functional, able to live more active lives alongside their caregivers, and were not inconvenienced by chemotherapy clinics and hospitals. Patients expressed confidence in this treatment, as many achieved drastic tumor shrinkage, which included an effect on brain metastases. One patient had 10 small brain tumours, which all disappeared after 6-8 weeks on ceritinib.

Patients placed on alectinib saw a reduction in tumor size, as well as relief from common symptoms associated with advanced lung cancer; as described by one patient in the LCC submission, "It allowed me to live". Alectinib delayed and prevented the use of radiation therapy and thus possible cognitive damage, which can result following chemoradiation therapy. Side effects did not inhibit daily activities, and due to the treatment modality being oral, patients and their caregivers were not burdened or inconvenienced with long hospital visits or recuperation time. Patients were able to return to work or stay at home to care for their family. LCC highlighted that other treatments may impose financial and physical burdens on the patients and their caregivers.

According to OLA, treatments used by the five patients with lung cancer included: Spiriva, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza and Ventolin (as needed). One patient reported undergoing radiation and another was the recipient of a double lung transplant earlier in 2018. One patient did not provide a response as that patient indicated that there were too many treatments to list. OLA reported that current treatments do provide some relief for fatigue, shortness of breath,

cough, appetite loss and low energy. However, certain side effects, which include palpitations, dry mouth, mouth sores, light-headedness, dizziness, shakiness, and impact on mood, need to be better managed. Other side effects included loose bowels, headaches, and difficulty sleeping, with one patient stating the weight of oxygen tanks being problematic.

Many patients described the financial burden associated with the treatments in the OLA submission. Patients who were unable to work had to live on a fixed income, making the purchase of nutritional food difficult as it is more expensive. In addition, patients who were no longer able to drive, but were on treatments associated with many appointments had the additional financial burden of paying for cabs. The desire of fewer medical appointments was a common theme. The multi-generational impact of loss of income was illustrated by one patient, whose daughter was forced to stop working to care for her mother.

None of the respondents interviewed by the OLA, including patients with advanced disease, considered the idea of not being treated. Several respondents stated the need for clear communication and information regarding the disease and available treatment options to help patients cope with their condition and help their decision-making process. Patients felt that general practitioners (GPs) needed to know more about lung diseases to avoid unnecessary delays in treatment and diagnosis, and suggested that there is a need to train GPs.

Improved outcomes:

LCC noted that targeted therapies have changed the disease paradigm for patients with lung cancer and it is no surprise that patients value treatments with manageable side effects that will provide an extension of life and quality of life. Expectations for treatments for patients with ALK-positive lung cancer have increased due to patients' experiences with crizotinib; patients hope to maintain a high level of functionality, be able to continue to parent, work, maintain family life, and enjoy life (e.g., travel and go on vacation). LCC reported on the experience of one patient with ALK-positive lung cancer who has been living with lung cancer for 10 years and was able to get married, buy a house, work to support a mortgage, and travel.

LCC further noted, that caregivers value and welcome the independence that patients are able to achieve. This allows them to continue to work and co-manage a family unit with a partner who is well.

OLA reported that overall patients desire treatments that will increase independence, require less assistance from others, and improve energy. According to OLA key treatment outcomes of lung cancer that patients and their caregivers would like to see addressed are: stopping or slowing the progression of the disease, reducing pain, fatigue, cough and shortness of breath, and improving appetite and energy. Patients and caregivers would like to see the following current side effects reduced or eliminated: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. Patients and caregivers would also value less or no burden of cost associated with new treatments.

OLA further noted that quality of life, not just extension of life, is a theme that continually came through from patients. Patients would value the administration of treatments at home, which would lead to less disruption of their daily routine by removing the need to take time off work. There is also the desire for more respiratory and lung cancer specialists and a better coordinated health system.

3.1.3 Impact of Lung Cancer and Current Therapy on Caregivers

The impact of lung cancer and current therapies was discussed in the LCC submission. Impact on caregivers was not reported in the OLA submission. According to LCC the diagnosis of lung cancer can be devastating and with a survival rate of 17% of patients, caregivers worry that the diagnosis of cancer is synonymous to a death sentence. Moreover, caregivers often feel the need to take "*ownership for protecting their loved ones*" and as a result take on several negative emotions, including a high level of mental stress, anxiety, worry, depression, and psychological distress that can lead to a lower quality of life for both caregivers and patients. The FOLCR survey revealed caregivers felt the weight of lung cancer more acutely than patients themselves, and worried about the extent of disease and ultimate outcome at the time of diagnosis. Caregivers experienced negative implications and unconscious attitudes towards lung cancer, which made them feel emotionally burdened and isolated.

Caregivers of patients on chemotherapy lost time at work, with over half (59%) reducing the number of hours worked and 8% quitting their jobs, in order to ensure the proper management of their loved ones. This included taking loved ones to appointments, while having to juggle other needs at work and at home.

Caregivers of patients on immunotherapy and targeted therapies, reported that side effects were fewer and manageable. Patients were able to get out of bed, go for their appointments by themselves and even go back to work, which enabled caregivers to continue working.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Brigatinib

Information on patient experiences with brigatinib are reported on behalf of respondents in the LCC submission, as OLA's patient group did not have experience with brigatinib. LCC provided the perspective of 5 patients and 4 caregivers with experience with brigatinib. Three key themes emerged from the patient experience with brigatinib: (i) it was effective in controlling cancer (including brain metastases), (ii) it had manageable side effects, and (iii) it allowed continuation of life with good quality.

Three patients reported brain metastases that either shrunk or went away with brigatinib treatment. One patient had two courses of chemotherapy, was subsequently diagnosed with ALK-positive disease, was put on crizotinib, and the MRI showed multiple nodules in the brain. After initiation of brigatinib that patient stated: "*Scans show everything is shrinking and disappearing, it is doing its job.*" That patient's follow up scans for the next year showed stable disease with side effects such a diarrhea and constipation and some mild pain issues that the patient managed with exercise. According to LCC that patient is thankful for each day. Another patient reported 80% shrinkage in the lung tumor, favourable activity in the lymph nodes and bone metastases, and all brain metastases were gone at the four week mark. Another patient became resistant to crizotinib, was put on brigatinib, and the brain metastasis improved and the cancer remained stable.

Two caregivers reported that brigatinib was used to overcome disease resistance to crizotinib. One of the caregivers takes care of her 15 year old son who showed no evidence of disease on crizotinib for two years, subsequently developed new brain lesions, and is currently on brigatinib. He is tolerating the treatment well with very few side effects.

Many patients on second line brigatinib were reported to have remained stable. LCC indicated that data have shown patients have a substantial improvement in median progression-free

survival compared to current standard of care. LCC suggested that patients who received brigatinib as a second-line treatment had a median overall survival of over 27 months from the time of the start of brigatinib (with a median progression-free survival of 11 months while on prior crizotinib, based on multiple PROFILE trial data).

Common side effects of brigatinib included fatigue, vomiting, diarrhea, constipation, abdominal pain, and muscle and joint pain. Patients reported that these side effects were quite manageable. Two patients reported tolerating brigatinib better than crizotinib, with one patient still able to work full-time with stable disease. That patient experienced an increase in blood pressure and elevated creatinine kinase, was reduced from a 180mg to a 120mg dose on brigatinib, and his scans are currently stable. The other patient reported that, whereas side effects with crizotinib included flu-like symptoms that lasted for weeks, side effects with brigatinib were easier to tolerate with less fatigue, minimal swelling and less constipation. LCC noted that brigatinib has been a great drug for that patient. Additionally, two patients experienced diarrhea, with one of them reporting the use of imodium to help with these symptoms and the other patient reporting experiencing vomiting.

According to LCC brigatinib allowed patients to enjoy life's activities. LCC provided two examples of patients who continue an active life style while receiving brigatinib. One patient was a very active person who hiked, biked and swam regularly prior to his diagnosis. After chemotherapy and crizotinib, he was put on brigatinib and is still able to continue the activities he enjoys. A caregiver reported the experience of the other patient, who was on crizotinib for 10 months but due to brain metastases was switched to brigatinib. Though the patient experiences fatigue and naps a lot, that patient continues to ride the bike for 45 miles at least 3 times a week and recently celebrated the five year cancerversary. The caregiver stated: *"While he does experience some side effects with brigatinib, it does not stop him from doing what he wants. We travel with no problems. He says, 'I may have cancer, but cancer does not have me'."*

According to LCC brigatinib allows patients the continuation of quality of life. LCC highlighted the importance of new and better treatments that provide the opportunity to extend survival, prolong life and give patients hope for the future. LCC noted the need for new treatments given that many patients will eventually relapse. One patient reported that new treatments provide the opportunity and time to move from one bridge to the other, time to spend with loved ones, and the opportunity to wait for new treatment options. LCC concluded that providing patients with new and better treatment options [such as brigatinib] enables them to live, and importantly live well, while hoping for better and longer lasting treatment options with minimal side effects, to become available.

3.2.2 Companion Diagnostic Testing

LCC stated that patients for this indication would already have been tested for the ALK biomarker before treatment with crizotinib. As a result, companion diagnostic tests would not be required, and in turn, would not pose a burden on the healthcare system.

3.3 Additional Information

The LCC outlined that there are first and second line options in the ALK-positive lung cancer space and that this submission is targeting the need for another second line option.

LCC also reported that clinical data show that patients on brigatinib have a higher median progression-free survival than both 2nd line ceritinib and 2nd line alectinib; this delay in disease progression aligns with patient values. In addition patients' experience with brigatinib shows that it allows patients to maintain the same high quality of life as they have on their first line ALK inhibitor. However, the LCC recognizes that this is based on phase II data, and

hence, comes with a degree of uncertainty. LCC recommends that pCODR considers a conditional approval as phase 3 data is pending. Specifically, the LCC mentioned they are currently working with physicians to establish a national lung registry that will help provide real world evidence (RWE) on treatments, and there is a study ongoing to collect RWE on patients with ALK-positive disease. From the perspective of LCC, for patients with advanced ALK-positive NSCLC, new and better treatments are a necessity because many patients will eventually relapse. The introduction of additional treatments into the market place makes price negotiations more competitive and helps to better manage costs in the publicly funded healthcare system. LCC noted that alectinib (currently 2nd line treatment) is in pricing negotiations and may become the preferred first line option due to clinical data demonstrating superiority over crizotinib. LCC suggests that pCODR considers the impending availability of alectinib in the first-line in their recommendation so that patients placed on first-line alectinib are also able to take advantage of a second line option.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

Input was obtained from the eight of the nine provinces (Ministries of Health and/or cancer agencies) 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:

- Indication creep into first-line treatment
- Comparative data to ceritinib as well as alectinib

Economic factors:

- Additional costs to manage and treat adverse events

Please see below for more details.

4.1 Currently Funded Treatments

Currently, the standard second-line therapy for patients with ALK-positive NSCLC who have failed crizotinib would be chemotherapy (docetaxel, platinum doublet or pemetrexed) or immunotherapy (nivolumab or pembrolizumab). At the time of the PAG input, ceritinib is funded in some jurisdictions and alectinib has been recently reviewed at pCODR.

PAG noted that the AP26113 trial compared two different dosing regimens of brigatinib. PAG is seeking information on whether comparison data is available comparing brigatinib to ceritinib as well as alectinib.

4.2 Eligible Patient Population

Although NSCLC is a common cancer, brigatinib would only be indicated for patients with ALK positive NSCLC and who have progressed on or are intolerant to an ALK inhibitor (crizotinib), which would be a small number of patients. PAG noted that an oral ALK inhibitor with CNS activity would fill a gap in therapy for patients who have CNS metastasis and failed crizotinib therapy.

Alectinib for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC was recently reviewed at pCODR. PAG noted that alectinib will likely become the standard first-line treatment option and is seeking guidance on the use of brigatinib following first-line treatment with alectinib.

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

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

PAG noted that if intolerance to crizotinib is not defined, there would be a lower threshold of tolerance to crizotinib and patients may be deemed intolerant after a one dose. If brigatinib is demonstrating better benefits than crizotinib, brigatinib would essentially replace crizotinib as first-line treatment. PAG also noted there is a phase III trial (ALTA-1L) comparing brigatinib and crizotinib in previously untreated ALK-positive NSCLC. Overall, there is a strong potential for indication creep with brigatinib into the first-line setting. PAG noted that brigatinib in previously untreated ALK-positive NSCLC is out of the scope of this current review.

4.3 Implementation Factors

Brigatinib's dosing schedule is 90mg orally once daily for the first seven days, if 90mg is tolerated during the first seven days, the dose is increased to 180mg orally once daily. The dosing schedule is different from the other ALK inhibitors available. The one week dose escalation phase is a barrier to implementation as it could lead to dosing errors and patient confusion.

Brigatinib is an oral tablet with multiple strengths, dose adjustment is accomplished by adjusting the number of tablets to take. This is an enabler to implementation. However, PAG noted there may be a potential for drug wastage for dose adjustments from 180mg back to 90mg daily.

PAG is seeking clarity on treatment until "disease progression", treatment duration and treatment discontinuation.

As brigatinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation. Additional pharmacy resources will be required for drug preparation, administration time, and monitoring for multiple severe adverse effects including pulmonary toxicity (i.e., interstitial lung disease) and drug-drug interactions. PAG also noted some patients may require emergency treatment for interstitial lung disease.

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, where patients can take oral drugs at home. PAG identified the oral route of administration as an enabler to implementation.

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

4.4 Sequencing and Priority of Treatments

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

PAG noted clinicians may prefer to use available ALK inhibitors sequentially rather than alternatively. PAG is seeking clarity on the use of brigatinib in later lines of therapy, for example, as third-line treatment following second-line ceritinib and first-line crizotinib. PAG is also seeking guidance for patients who do not tolerate second-line ceritinib and whether

switching to brigatinib would be appropriate. Similarly, for patients who do not tolerate brigatinib, whether it would be appropriate for these patients to switch to ceritinib.

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

pCODR received two group clinician inputs (representing 9 clinicians) on brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non–small cell lung cancer (NSCLC) who have progressed on or who were intolerant to an ALK tyrosine kinase inhibitor (TKI) (crizotinib). A joint input from seven oncologists from Lung Cancer Canada (LCC) and two oncologists from Cancer Care Ontario (CCO) was submitted.

The clinicians providing input noted that for the present indication, the most relevant comparators to brigatinib would be ceritinib or alectinib (the latter depending on availability). It was also noted by clinicians from the LCC that in provinces where ceritinib is not funded, the current standard of care is platinum-based doublet therapy. The clinicians from both groups agreed that the eligible patient population in clinical practice aligns with the patient population in the ALTA trial. Clinicians from LCC further suggested that brigatinib would be an excellent alternative in patients who are intolerant to crizotinib. According to the clinicians from LCC, brigatinib addresses an unmet need in the target population as alternative therapies for second-line treatment following progression on crizotinib provide smaller gains in progression–free survival (PFS) than brigatinib. The clinicians from CCO noted that the present unmet need will be addressed once alectinib is available. This group indicated that once alectinib is available, most clinicians will chose alectinib as 1st line therapy or post progression on crizotinib. Clinicians from LCC reported their clinical experience of using brigatinib after crizotinib, which showed favourable PFS and toxicity results compared with their institutional experience of using ceritinib after crizotinib. There was some discrepancy between the clinician groups regarding the sequencing of current drugs for the treatment of locally advanced or metastatic NSCLC. The LCC group indicated that brigatinib would replace ceritinib as second-line treatment after crizotinib unless otherwise contraindicated. This group further noted that each of the ALK TKIs have specific toxicity profiles, and thus have potential benefit and roles depending on patient comorbidities and specific circumstances. The clinicians from CCO indicated first-line preference as alectinib or ceritinib. This group further noted that brigatinib, ceritinib, or alectinib are options in second-line, however, there is currently insufficient evidence to recommend one over the other.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for this Type of Cancer

In the joint clinician input from LCC it was stated that ceritinib is the most appropriate comparator in 2nd line. However, in provinces where ceritinib is not funded the current standard of care is platinum-based doublet therapy (commonly platinum drug in combination with pemetrexed for ALK-positive NSCLC with non-squamous histology). It was also suggested that in special circumstances, for individuals who may not tolerate doublet chemotherapy, single agent chemotherapy or immunotherapy (in patient with positive (>50%) PDL1 staining) are alternative treatment options. Clinicians from CCO, stated that they would use alectinib in 2nd line post progression on crizotinib; although it has been recommended by pCODR for reimbursement, at the time of this input, it is not currently funded in Ontario.

According to the clinicians from LCC, other standard treatment options are immunotherapies, including nivolumab or pembrolizumab, which have been approved for funding in multiple provinces. The clinicians indicated that these options are typically used as last line of therapy, after all ALK TKIs and chemotherapy have been exhausted, regardless of PD-L1 test results.

5.2 Eligible Patient Population

The clinicians agreed that the eligible patient population would include patients with locally advanced or metastatic ALK-positive NSCLC who have progressed on crizotinib, with or without prior chemotherapy for metastatic disease. The clinicians from LCC suggested that brigatinib would also be an excellent alternative in patients who are intolerant to crizotinib, even if there has not been disease progression.

The clinicians from LCC mentioned that an unmet needs exists for a drug such as brigatinib which shows substantial improvements in median progression-free survival (PFS) compared to current standard of care options; nothing none of the currently therapies increases the median PFS by more than one year. The clinicians felt that PFS is an appropriate surrogate outcome for overall survival (OS) in this setting, as the availability of multiple ALK TKIs after progression may confound comparative OS estimates. It was estimated that patients who would receive brigatinib in second-line would have a median OS of over 27 months from the time of the start of brigatinib (with a median PFS of 11 months while on prior crizotinib, based on multiple PROFILE trial data). Clinicians felt that these long median OS estimates further provide support for PFS surrogacy.

The clinicians from CCO agreed that there is an unmet need, which will, however, be addressed once alectinib is funded following the positive pCODR reimbursement recommendation. The clinicians indicated that they would use brigatinib in situations where alectinib is not available.

All clinicians agreed that the inclusion and exclusion criteria of the study population are applicable to clinical practice, for example, patients with an ECOG status 0-2, and there are no subgroups in the patient population to limit the use of brigatinib. The clinicians from LCC noted that patients with high levels of oxygen supplementation should consider brigatinib only after the failure of alternative treatments, and those on an ALK TKI should stop 7 days prior to initiation of brigatinib because of the greater risk of developing early onset pulmonary events. As these events typically occur within two to three days of drug initiation, starting patients at the beginning of the week is recommended, so that the greater risk period of developing an early onset pulmonary event occurs during the work week.

5.3 Relevance to Clinical Practice

The clinicians from CCO did not report experience with brigatinib, but did indicate there were no concerns or contraindications to its use, and it would be preferable to chemotherapy in almost any clinical scenario as a 2nd line therapy due to the evidence in terms of response rate, duration of response, CNS activity, and safety profile. They noted some patients who are unfit for chemotherapy, could potentially tolerate brigatinib. They also indicated that once alectinib is available, most clinicians will choose alectinib as 1st line therapy or post progression on crizotinib. The remainder of this section is reported on behalf of the LCC clinician group input.

Clinicians from LCC had experience treating seven patients with brigatinib, of which four patients were treated through clinical trials. Of these seven patients, four were treated after failure on crizotinib (2nd line); one was treated after failure on crizotinib and alectinib; one was treated after failure on crizotinib, ceritinib, and alectinib; and one patient was treated in the first line setting (treatment naïve). Four patients had brain metastases at the initiation of brigatinib. One patient (the most pre-treated patient with prior crizotinib, ceritinib, and alectinib) was on baseline oxygen supplementation (3L/min) and developed an early onset pulmonary event, was re-challenged, and developed the event a second time. According to the clinicians this patients should not have been given brigatinib in the first place due to baseline

oxygen supplementation (3L/min). Therefore, the treatment effect of brigatinib could not be assessed in this patient. Of the six evaluable patients, four patients experienced a partial response and two patients had stable disease. The PFS for patients with a partial response was 11 months for two patients (one of the patients had been in the 90 mg arm of the ALTA trial), 20 months for one patient, and has not been reached in one patient who remains on the drug at 15 months. The PFS for the two patients with stable disease was 19 months and has not been reached in one of the patients at 13 months after starting brigatinib. None of the patients required dose reduction.

Four patients experienced oligoprogression that was amenable to alternative local therapy (such as stereotactic radiation) or observation, and thus, were continued on brigatinib post-progression up to 1, 2, 4, and 6 months, respectively. The clinicians indicated allowing treatment beyond progression can be beneficial if determined to be of continued benefit. All other patients had systemic disease progression across multiple organs.

Health related quality of life was assessed using the European Quality of Life Five Dimensions scale (EQ-5D-5L) questionnaire in four patients while on brigatinib therapy. The mean utility score was 0.81 for all four patients.

Three patients were retired at the time of brigatinib initiation, two patients continued to work full-time, and two patients returned to work part-time. Two patients took once-in-a-lifetime vacations, including an Antarctic vacation and a hiking trip in Europe.

The clinicians highlighted that based on personal and published reports of ceritinib in second-line, brigatinib was significantly better tolerated (significantly lower gastro-intestinal toxicity and substantially lower probability of hepatotoxicity), and had significantly longer PFS compared with 2nd-line ceritinib. This was supported in their local experience from the six evaluable patients on brigatinib with PFS results that were in the double digit months; which is significantly longer than the PFS results obtained from 21 patients who were treated with ceritinib after crizotinib failure at their institution. In addition it was noted that out of those 21 patients, 14 required dose reductions, mostly for asymptomatic hepatic transaminitis, and 15 patients had grade 2 or higher gastrointestinal toxicity.

The clinicians further noted that brigatinib fares even more favourable when compared with platinum-doublet chemotherapy (with maintenance pemetrexed) in terms of severity and frequency of toxicities, median PFS, response rates, disease control rates, and duration of therapy. In the absence of direct comparative data, the clinicians notes that this comparison was based on extrapolations from first-line trial data of platinum-pemetrexed (with maintenance) in NSCLC patients.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Both joint clinician inputs agreed the use of brigatinib is an appropriate second-line therapy after failure on (or intolerance to) crizotinib in ALK-positive NSCLC patients, unless otherwise contraindicated. The clinicians from LCC indicated brigatinib would replace ceritinib as second-line treatment (unless otherwise contraindicated), and the clinicians from CCO indicated it would replace chemotherapy (the only currently funded second-line treatment in Ontario). The clinicians from LCC noted that each of the ALK TKIs have specific toxicity profiles, and thus have potential benefit and role depending on patient comorbidities and specific circumstances.

5.5 Companion Diagnostic Testing

The clinicians noted that current practice includes routine ALK testing on all NSCLC patients. No concerns about the ALK testing strategy were expressed by clinicians. The clinicians from

LCC reported that the Canadian standard is to perform immunohistochemistry staining for the ALK protein, which takes on average one to two days after a diagnosis of NSCLC. It is reported to be an inexpensive test, and only 1-2% of immunohistochemical tests for ALK require FISH confirmation.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 Please consider the optimal sequencing of treatments for patients with ALK-positive NSCLC, specifically: ALK TKIs (crizotinib, alectinib, ceritinib), chemotherapy, and immunotherapy (in clinical practice, if brigatinib was available).

There was some discrepancy in the sequencing and priority of all current drugs for the treatment of locally advanced or metastatic NSCLC reported by the two clinician groups. The clinicians from LCC indicated funding for first-line treatment is crizotinib, second-line should be brigatinib, third-line should be chemotherapy (platinum-doublet; if non-squamous histology, platinum-pemetrexed), followed by fourth-line docetaxel, nivolumab, or pembrolizumab. The clinicians from CCO indicated first-line preference as alectinib or ceritinib. This group further noted that brigatinib, ceritinib, or alectinib are options in second-line, however, there is currently insufficient evidence to recommend one over the other. It was suggested that lorlatinib could also be an option, based on phase II data showing high response rates for lorlatinib post 2nd generation ALK TKIs.

5.7.2 What would your preference be for second-line ALK TKI (i.e., brigatinib, alectinib, or ceritinib) following crizotinib? Please comment on the preference considering patient preference, efficacy, safety, and administration.

The clinicians from LCC indicated the preference for a second-line ALK TKI following crizotinib would be brigatinib. This clinician group also highlighted that patients with ALK-positive disease are a relatively unique patient population in that median PFS results across trials by drug and by line of therapy show consistency regardless of the ethnicity of the patients enrolled (Caucasian European, North American, or Asian). This consistency may be intrinsically related to the biology of the disease. The clinicians noted that due to the observed consistency one could reasonably perform a cross-trial comparison in which brigatinib shows the longest median PFS compared with ceritinib (median PFS ranged from 6-8 months) or alectinib (median PFS ranging from 8.5-10 months) in the second-line setting after failure of crizotinib. In order to provide a further example for the consistency of results in patients with ALK-positive disease, the clinicians noted that first line crizotinib in multiple trials across different continents and ethnicities has demonstrated virtually identical median PFS results of around 11 months.

The clinicians from CCO indicated that post-crizotinib, phase III trial data support the use of ceritinib or alectinib over chemotherapy, but it is not clear if one is superior.

5.7.3 Is there preference as well as evidence to support sequencing of second-generation ALK TKIs (e.g., alectinib or ceritinib followed by brigatinib) in patients who have progressed on or who were intolerant to crizotinib?

Both clinician groups indicated there is no data to support sequencing of second-generation ALK TKIs (e.g., alectinib or ceritinib followed by brigatinib) in patients who have progressed on or who were intolerant to crizotinib.

5.7.4 In jurisdictions where there is no publically funded ALK TKI in the second-line setting, would brigatinib in the third-line setting following second-line chemotherapy and first-line ALK TKI be considered?

The clinicians from LCC reported there was no rationale to sequence first-line crizotinib, second-line chemotherapy, and third-line brigatinib. They reported that brigatinib provides disease control (stable disease + partial response + compete response) in >90% of patients in the second-line setting, has shown a median PFS of over 15 months, and is well tolerated. In contrast, the clinicians reported that doublet chemotherapy has a substantially lower (<50%) disease control rate, and a median PFS of under 6 months based on extrapolated data from the chemotherapy-naïve population. They also conveyed the risk that patients may become too sick from the toxicity and ineffectiveness of second-line chemotherapy, and thus may not be eligible for third-line brigatinib.

The clinicians from CCO indicated they would definitely use brigatinib in third-line if no other ALK TKI was funded following second-line chemotherapy and first-line crizotinib.

5.7.5 If a patient discontinued an ALK TKI such as ceritinib in the second-line setting due to adverse events or intolerance, would you offer brigatinib?

Both groups agreed that in the event a patient discontinued an ALK TKI (such as ceritinib) in the second-line setting due to adverse events or intolerance, they would offer brigatinib (if no contraindications). The clinicians from LCC noted that each of the ALK TKIs have potential different roles in patients who have become intolerant to another ALK TKI, and should be prioritized depending on the patient comorbidity profile. For example, in cases of high levels of oxygen supplementation, alectinib or ceritinib may be preferred over brigatinib, whereas in cases of hepatic transaminitis with alectinib or ceritinib, brigatinib may be preferred.

5.7.6 Please comment on the number of ALK TKIs a patient should receive in their treatment trajectory for ALK-positive NSCLC.

Both clinician groups agreed a patient should receive at least two ALK TKIs in their treatment trajectory. The clinicians from LCC suggested that ideally, patients should have access to each ALK TKI at least once in their lifetime, as there is a role for each ALK TKI depending on patient circumstances (comorbidities, toxicities to current or prior ALK TKIs, etc.). They further commented that ALK-rearranged lung cancers are aggressive, and patients who progress on specific ALK TKIs can be identified quickly through imaging and clinical worsening of symptoms. Patients can then be sequenced to the next available ALK-inhibitor until all ALK-inhibitors have been exhausted. They also noted that lorlatinib, a third-generation ALK-inhibitor, may be effective in patients who have failed multiple ALK inhibitors. By way of clinical experience, the clinicians reported having seen responses to a fourth and fifth ALK TKI.

The clinicians from CCO indicated there should be access to at least two ALK TKIs, either (1) crizotinib followed by a 2nd generation ALK TKI or (2) alectinib or ceritinib followed by lorlatinib.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of brigatinib as a monotherapy in adult patients with anaplastic lymphoma kinase positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib.

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

- Critical appraisal of submitter-provided indirect treatment comparisons (naïve ITC, MAICs and NMAs) between brigatinib and ceritinib, alectinib, and single agent chemotherapy/

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1 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 pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection criteria for brigatinib systematic review for use in patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs Aggregate data from clinical trials investigating the safety and efficacy of brigatinib should be considered.	Patients with locally advanced or metastatic ALK+ NSCLC who have progressed on or who were intolerant to crizotinib. (second-line treatment) <u>Subgroups:</u> • ECOG PS (0 vs. 1, or 2) • Age (< 65 years vs. ≥65 years) • Ethnicity (Asian vs. non-Asian) • Sex • Smoking status (never or light vs.	Brigatinib MonotherapyOral daily dosing 180 mg (with 7-day lead-in at 90 mg)	Cytotoxic Chemotherapies for ALK+ NSCLC Cisplatin-based or Carboplatin based combination therapy with Pemetrexed or Docetaxel Paclitaxel Crizotinib Alectinib Ceritinib	<u>Primary</u> • **OS** • **PFS** • **HRQoL** <u>Secondary</u> • ORR • cORR • CR • PR • DOR • DCR • OCRR • IDCR • DOIR Safety • **AEs** • SAEs • WDAEs • GI toxicity

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	current/heavy smokers) • Brain metastases vs. no brain metastases • Previous chemotherapy			• Hypertension • Hepatotoxicity • ILD/pneumonitis • Hyperglycemia
AE=adverse events; ALK=anaplastic lymphoma kinase; CORR=confirmed objective response rate; CR=complete response ; DCR=disease control rate; DOIR = duration of intracranial response; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; GI=gastrointestinal; HRQoL=Health related quality of life; IDCR=intracranial disease control rate; ILD=Interstitial lung disease; OCRR=overall cranial response rate; CORR=confirmed objective response rate; ORR=overall response rate; PR=partial response; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawals due to adverse events				

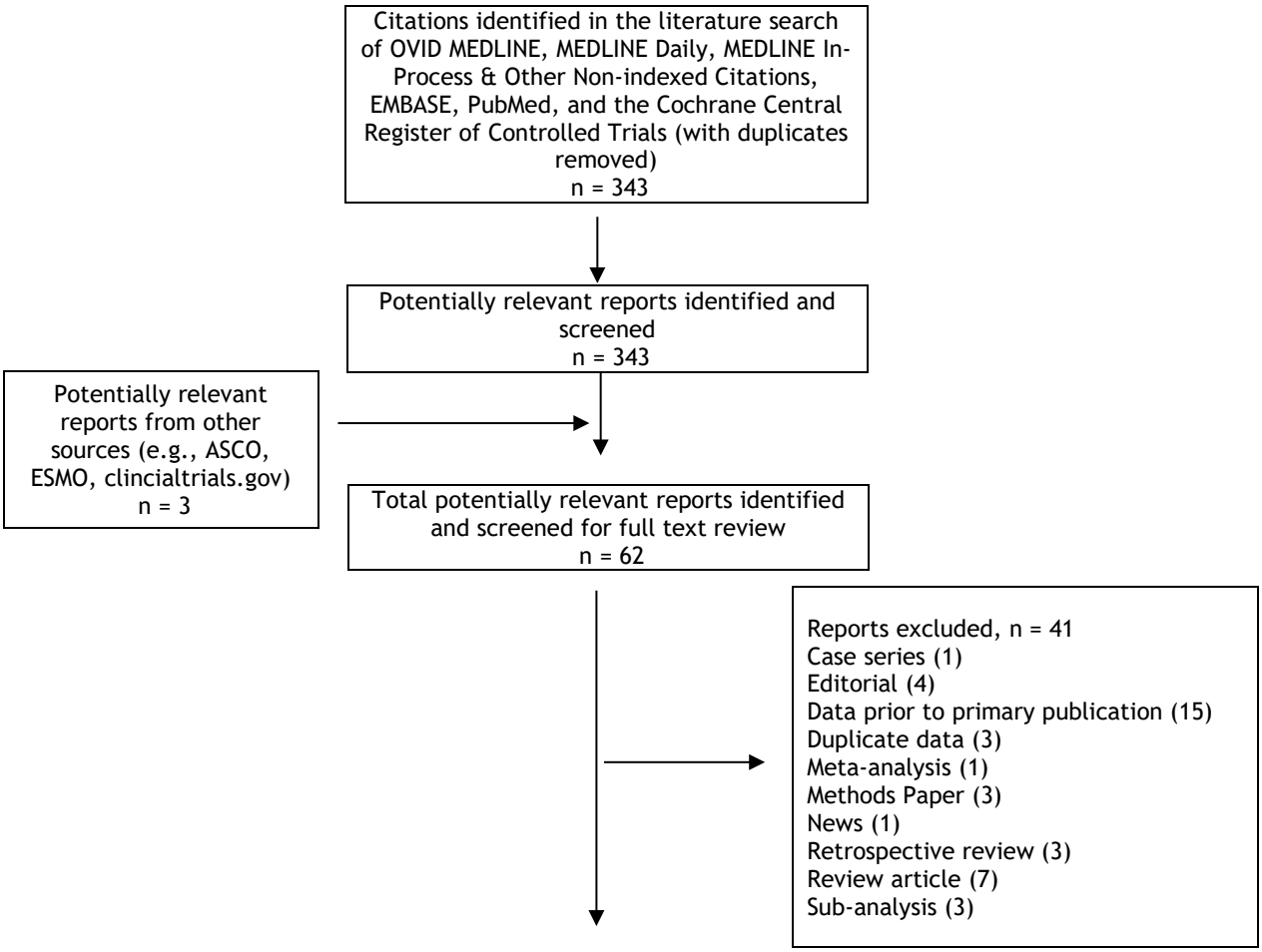
* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 343 potentially relevant reports identified, 62 full text citations were reviewed. An additional 3 potentially relevant reports were identified. From these full text citations 41 records were excluded following full text review, the remaining 21 citations were identified to contain data from 2 primary studies.[1,2] The included citations were grouped according to the primary studies and sorted according to the data cut-off date and were included in the pCODR systematic review with the study.[1,2] One combined analysis of trial data from both studies was also included in the review.[3] Studies were excluded because they were a case series,[47] editorials,[48-51] data published prior to primary publication,[52-67] duplicate data already available in published papers,[68-70] a meta-analysis,[71] methods papers,[72-74] news report,[75] retrospective reviews,[24,76,77] review articles,[78-83] and sub-analyses for other outcomes of the ALTA and Study 101 not within scope of the review.[84-86]

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of studies[87]



Reports presenting data from 2 clinical trials: ALTA trial and Study 101

ALTA Trial

Papers

- Camidge DR et al. 2018[3]
- Kim D-W et al. 2017[1,10,88]

Abstracts and Posters

- Ahn M et al. 2017[12,18]
- Ahn M et al. 2017[11]
- Camidge DR et al. 2017[89]
- Camidge DR et al. 2017[90]
- Hochmair et al. 2018[14]
- Huber et al. 2018[15,16]
- Kawata AK et al. 2018[91]
- Langer CJ et al. 2017[92]
- Langer C et al. 2017[93]
- Lenderking WR et al. 2017[94]
- Ou S-H et al. 2017[13]
- Reckamp KL et al. 2017[95]

- Clinicaltrials.gov (NCT02094573)[9]
- European Medicines Agency. Assessment report. Alunbrig. 2018[6]

Study 101

Papers

- Camidge DR et al. 2018[3]
- Gettinger SN et al. 2016[2,19]

Abstracts

- Bazhenova LA et al. 2016[5]
- Bazhenova LA et al. 2017[7]
- Bazhenova LA et al. 2017[4]

- Clinicaltrials.gov (NCT01449461)[96]
- European Medicines Agency. Assessment report. Alunbrig. 2018[6]

- pCODR Submission[17]
- Alunbig (brigatinib) Product Monograph[8]
- Tolley Health Economics[20]

**Note: Additional data related to studies* ALTA[1] and Study 101[2] *were also obtained through requests to the Submitter by pCODR*[17]

6.3.2 Summary of Included Studies

Two clinical studies were identified through the systematic literature review (ALTA [n = 222] and Study 101 [n = 137]). ALTA was a multicentre, randomized, open-label, non-comparative, phase 2 trial evaluating two dosing regimens for brigatinib in patients with crizotinib-refractory ALK-NSCLC.[1] The 101 trial identified was a multi-arm, open-label, dose-ranging phase 1/2 study of brigatinib in ALK-NSCLC and other malignancies.[2] A summary of the trial characteristics are outlined below for the entire study population included in the trials.

Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: ALTA (ALK in Lung Cancer Trial), Study 201[1] Protocol Number: AP26113-13-201 Non-comparative, Randomized, Open-label, multicentre, phase II trial. N= 222 randomized; n= 219 treated Number of centres = 71 and number of countries = 18 Patient Enrolment Dates: June 4, 2014 to September 21, 2015. Primary Data cut-off: February 29, 2016.[1,10] Primary Final Analysis Date: May 16, 2016[1] Second data cut-off Date: May 31, 2016[3,11] Third data cut-off Date: February 21, 2017[12,14,18] Long-term Analysis Data cut-off: September 29, 2017.[6,15,16] Funding: ARIAD Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	<u>Key Inclusion Criteria:</u> Eligible patients (18 years of age) had locally advanced or metastatic ALK-positive NSCLC, investigator determined disease progression while receiving crizotinib, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), adequate organ and hematologic function, and Eastern Cooperative Oncology Group performance status less than or equal to 2 <u>Key Exclusion Criteria:</u> History or presence of pulmonary	Dosage comparator Brigatinib Arm A: 90 mg once daily Arm B: 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]	<u>Primary:</u> Confirmed ORR per RECIST v1.1 (per investigator) <u>Secondary:</u> Confirmed ORR (per central IRC) CNS response (IRC-assessed intracranial confirmed ORR PFS inpatients with active brain metastases), Duration of response, PFS, Overall survival (OS), Safety, tolerability,

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Trial Registration: ClinicalTrials.gov NCT02094573[9]	interstitial disease or drug-related pneumonitis, or symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids Must not have received any prior ALK inhibitor other than crizotinib; crizotinib within 3 days of the first brigatinib dose; cytotoxic chemotherapy, investigational agents, or radiation therapy (except stereotactic [body] radiosurgery) within 14 days; or monoclonal antibodies within 30 days		Patient-reported symptoms of lung cancer health-related quality-of-life (QoL) scores assessed with the European Organisation for Research and Treatment of Cancer QoL questionnaire (EORTC QLQ-C30, version 3.0), including mean transformed global health status/QoL score (on the basis of questions 29 and 30)
Study: Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label phase 1 / 2 trial. Study 101.[2,19] Protocol Number: AP26113-11-101 Open-label, non-randomized, phase 1 - dose-escalation, phase 2 - expansion trial N = 137; Phase 1 (N=66); Phase 2 (N=71) N=79 (58%) ALK-rearranged NSCLC Number of centres = 9 and number of countries = 2 Patient Enrolment Dates: September 20, 2011 to July 8, 2014. Primary Data cut-off Date: June 15, 2015.	<u>Key Inclusion Criteria:</u> Phase 1: patients with histologically confirmed advanced malignancies other than leukemia. Phase 2: Five histologically and molecularly defined cohorts: 1. ALK inhibitor-naive *ALK*-rearranged NSCLC, 2.crizotinib-treated *ALK* rearranged NSCLC, 3. *EGFR*T790M-positive NSCLC	<u>Dosage comparator</u> Phase 1: Once daily regimens 30 mg once daily, with escalated doses to 60 mg, 90 mg and 120 mg, then to 180 mg, 240 mg and 300 mg once daily. Alternative dosing of twice-daily regimens of 60 mg, 90 mg and 120 mg. Phase 2: 90 mg, 180 mg and 180 mg with a 7 day lead in at 90 mg.	<u>Primary:</u> Phase 1: To establish the recommended phase 2 dose. Phase 2: ORR investigator assessed as per RECIST v1.1 <u>Secondary:</u> Confirmed ORR (per central IRC) PFS,

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Second Data cut-off Date: November 16, 2015[5] Third Data cut-off Date: May 31, 2016[4,6] Long-term Data cut-off Date: February 21, 2017[7] Funding: ARIAD Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited Trial Registration: ClinicalTrials.gov NCT01449461[96]	and resistance to one previous EGFR tyrosine kinase inhibitor, 4. other cancers with abnormalities in brigatinib targets (eg, ALK or ROS1), 5.crizotinib-naive or crizotinib-treated *ALK*-rearranged NSCLC with active, measurable, intracranial CNS metastases Eligible patients (18 years of age) Measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) Eastern Cooperative Oncology Group performance status of 0 to 1. A minimum life expectancy of 3 months or longer. No limit on the number of previous systemic therapies. <u>Key Exclusion Criteria:</u> Substantial uncontrolled or active cardiovascular disease or uncontrolled hypertension (diastolic blood pressure of >100		Duration of response, Overall survival (OS), PFS inpatients with active brain metastases), CNS response (IRC-assessed intracranial confirmed ORR Safety, tolerability,

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	mm Hg or systolic blood pressure of >150 mm Hg). Patients must not have received an investigational agent, systemic anticancer therapy (other than a reversible tyrosine kinase inhibitor), or radiotherapy 14 days or fewer before initiating brigatinib; allowed reversible tyrosine kinase inhibitors (eg, crizotinib, erlotinib, or gefi tinib) up to 72 h before initiation of brigatinib, if the patient was free of treatment-related toxicity.		

Table 6.3: Select quality characteristics of included studies of brigatinib in patients with ALK-positive non-small cell lung cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
ALTA Study [1]	Dose Comparison	Confirmed ORR per RECIST v1.1 (per investigator)	218	222	Not Stated in paper	Not stated in paper	No	Yes	ITT	No	Approved by the local institutional review board or ethics committee at

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
											each site
Study 101[2]	Dose Ranging	ORR per RECIST v1.1 (per investigator)	n/a	137	n/a	n/a	No	No	No	No	Approved by the relevant local review board or ethics committee

a) Trials

ALTA phase 2 trial[1]

One randomized, non-comparative, ongoing,[9] open-label clinical trial was identified that met the inclusion criteria.[1,10] The ALTA trial, also known as Study 201 or by its protocol number AP26113-13-201, was published by Kim et al in 2017.[1] This study is a dosage comparator evaluation. However, no statistical comparisons were planned between the two arms with respect to efficacy or safety. Patients were randomized to either Arm A, which received brigatinib 90 mg once daily or Arm B in which patients received brigatinib180 mg once daily with a 7-day lead-in period at 90 mg. This study was conducted at 71 centres across 18 countries including one centre in Canada.[1] For the purposes of this review only efficacy and safety data from Arm B will be examined, aligned with the current ALUNBRIG approved dosing regimen in Canada.[8] The trial Sponsor, ARIAD Pharmaceuticals Inc., a subsidiary of Takeda Pharmaceutical Company Limited., was the sponsor of the trial and was involved in the trial conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing and approval.

The primary data cut off for the ALTA trial was February 29, 2016 and the results of this analysis were published in Kim et al.[1] and posted on ClinicalTrials.gov.[9] The median follow-up time in months (range) for those individuals in Arm B was 8.3 (0.1 to 20.2) months.[1] Subsequent data extractions providing longer-term follow-up were conducted using data cut offs of May 31, 2016,[3,11] February 21, 2017[12,14,18] and September 29, 2017[6,15,16] providing a median (range) duration of follow of 24.3 (0.1 to 39.2) in the most recent analysis. Results abstracted from published papers[1,3] and abstracts,[11,12,14-16] an assessment report,[6] as well as material provided by the manufacturer are included in this review.[17,97]

Eligibility Criteria

Eligible patients (18 years of age) had locally advanced or metastatic ALK-positive NSCLC, investigator determined disease progression while receiving crizotinib, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), adequate organ and hematologic function, and Eastern Cooperative Oncology Group performance status (ECOG PS) of less than or equal to 2. Patients were excluded based on the following key exclusion criteria: history or presence of pulmonary interstitial disease or drug-related pneumonitis, symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids, any prior ALK inhibitor other than crizotinib, crizotinib within 3 days of the first brigatinib dose, cytotoxic chemotherapy, investigational agents, or radiation therapy (except stereotactic [body] radiosurgery) within 14 days; or monoclonal antibodies within 30 days.[1]

For a more detailed list of the key eligibility/exclusion criteria used in the trial refer to Table 6.2.

Outcomes

The primary outcome measure for the ALTA trial was confirmed objective response rate by the investigator, as per RECIST v.1.1. Secondary outcome measures were confirmed ORR as per IRC, CNS response, as IRC assessed ORR or PFS, duration of response, PFS, OS, safety, tolerability and patient-reported symptoms of lung cancer and health related quality of life (QoL) as measured by the EORTC-QLQ-30.[1]

Randomization, Sample Size, and Statistical Analyses

A sample size of greater than or equal to 109 patients was calculated in order to provide 90% power to rule out an ORR of 20% when the true ORR is greater than or equal to 35%. A two sided alpha level of 0.025 was used adjust for the fact that a test of each dosing regimen was performed. Patients were randomly assigned 1:1 to each of the two groups stratified based on baseline characteristics of presence of brain metastases and best-response to crizotinib (either CR or PR) as assessed by the investigator.[1] No statistical comparisons were planned between arms A and B with respect to efficacy or safety as the study was not prospectively powered for these comparisons. Multiple exploratory analyses were conducted with the results from the ALTA trial. These included evaluation within subgroups defined by age, sex, race, geographic region, mutation status, prior anticancer therapies, and other prognostic factors.[89] Continuous prognostic factors affecting the ORR were also examined using simple logistic regression models.[95]

101 phase 1 / 2 trial[2]

In addition to the ALTA trial,[1] an open-label, multi-arm, dose ranging, phase 1/2 study was conducted to inform the dose of brigatinib.[2] This study is also referred to as Study 101 or by its protocol number AP26113-11-101. In phase 1 of this study the dose for brigatinib was escalated with a starting dose of 30 mg up to total daily dose of 300 mg. The second phase, the expansion phase, of the study administered brigatinib in two regimens, 90 mg once daily and 180 mg once daily with a 7-day lead in period of 90 mg. Study 101 recruited 137 patients with only 79 patients (58%) having a diagnosis of ALK-positive NSCLC, of which 71 patients of the 79 had been previously treated with crizotinib. In the expansion phase, brigatinib was administered for the majority of patients in once daily dosing of 90 mg, 180 mg, or 180 mg with a 7-day lead-in of 90 mg.[2] Overall in the study, 66 patients were

recruited into the Phase 1 and 71 patients were enrolled in expansion phase. Only 18.2% of patients (25/137) enrolled in the study had been previously treated with crizotinib and received brigatinib aligned with the current dosing label of 180 mg with a 7-day lead-in of 90 mg.[2,4,5,7] All of the 25 patients were recruited into the expansion phase of the study as the dosing regimen provided was only employed in this phase of the trial.[2] This pCODR review will only present the data from these 25 patients, that align with the pCODR requested reimbursement criteria and the Health Canada approved dosing regimen for brigatinib. The trial sponsor's, ARIAD Pharmaceuticals, employees or representatives designed the study with input from the clinical investigators. The data collection, analysis and interpretation were funded by ARIAD Pharmaceuticals. All authors had access to the data.[2]

Eligibility Criteria

Patients were included in Phase 1 of the study with histologically confirmed advanced malignancies other than leukaemia. In the expansion phase of Study 101 patients were enrolled into five histologically and molecularly defined cohorts: (1) ALK inhibitor-naive *ALK*-rearranged NSCLC; (2) crizotinib-resistant *ALK* rearranged NSCLC, (3) *EGFR*T790M-positive NSCLC and resistance to one previous EGFR tyrosine kinase inhibitor, (4) other cancers with abnormalities in brigatinib targets (eg, ALK or ROS1), (5) crizotinib-naive or crizotinib-treated *ALK*-rearranged NSCLC with active, measurable, intracranial CNS metastases. Other eligibility criteria included: Eighteen years of age; measurable disease per RECIST v1.1 and ECOG of 2 or less. A minimum life expectancy of 3 months or longer.[2] The ECOG status criteria was subsequently amended to only include 0 or 1 according to the protocol amendments.[19]

Patients were excluded from Study 101 if they had substantial uncontrolled or active cardiovascular disease or uncontrolled hypertension (diastolic blood pressure of >100 mm Hg or systolic blood pressure of >150 mm Hg).[2]

Outcomes

The primary outcome measure for the Study 101 Phase 1 trial was to establish the dose recommendations for the expansion phase. For the first 4 cohorts the primary outcome was objective response rate by the investigator, as per RECIST v.1.1. For cohort 5, a primary outcome of CNS response was used. Secondary outcome measures ORR, PFS, OS, best target lesion response, best overall response, duration of response, safety and tolerability.[2] Only selected outcomes were reported for the subgroup of interest (N = 25).

Randomization, Sample Size, and Statistical Analyses

Study 101 was an open label, multi-arm, non-randomized, dose ranging study. Dose escalation in the first phase of the study was completed according to a 3+3 design permitting additional expansion of the utilization of doses to substantiate safety observations. Brigatinib was administered in 28 day cycles. Statistical assumptions were not pre-specified in the protocol. Pooled analyses were completed using phase 1 and expansion phase patients and included data from those individuals that received at least 1 dose of brigatinib. Although separate primary endpoints were defined in the protocol for the expansion phase, in the efficacy analyses patients from the dose-escalation phase were combined with those from the expansion phase matched on certain criteria such as tumor type, molecular subset and starting dose regimen.[2,19]

Determination of objective response rates in patients with ALK-positive NSCLC by previous treatment with crizotinib was a post-hoc analysis. The proportions of patients with ORR and exact binomial CI, as well as duration of response and PFS were calculated using the Kaplan-Meier method.[2]

Patients with Brain Metastases Analysis

In the systematic review, a third publication was identified that provides an exploratory analysis describing the clinical results for participants with brain metastases at baseline from the two above mentioned studies (ALTA and Study 101) of brigatinib.[3] The data cut-off for this analysis was May 31, 2016 for both trials.[3] Where applicable, for the ALTA trial patients in Arm B (N=110),[1] data analyses from this publication are also included in this pCODR review.[3] Update analyses have been published for this patient population for the data cut offs of February 21, 2017[12,13] and for September 29, 2017.[6,15,16]

b) Populations

ALTA phase 2 trial[1]

Patients were randomized between June 4, 2014 and September 21, 2015. During the enrollment time period, 222 patients were randomized in a 1:1 ratio to treatment Arm A or Arm B. For the purposes of this report only treatment Arm B (N = 110) will be discussed. The median age of participants in Arm B was 56.5 years (range: 20 to 81), with 58.2% female patients. The majority of patients enrolled were of ECOG performance 0 (40.9%) or 1 (27.3%). Adenocarcinoma was identified as the predominant tumor type 98.2%.[1,6] Most patients had 67.3% had brain metastases at baseline and received prior chemotherapy (74%).[1,3] Of the patients that received prior chemotherapy, 80 (72.7% of 110) had received prior-platinum based regimens.[1,6]

101 phase 1/2 trial[2]

Patients were enrolled between September 20, 2011 and July 8, 2014. Over this time period, 137 patients were enrolled in the study with 66 included in Phase 1 and 71 patients enrolled in the expansion phase. Of these patients 79 had ALK-positive NSCLC.[2] For the purposes of this report, only those individuals that were ALK-positive and resistant to crizotinib will be discussed (N=25).[4-7] The median age of the 25 participants was 57.0 years (range: 32 to 73), with 44 % female patients. The majority of patients enrolled were of ECOG performance 1 (60%) or 0 (40%). As with the ALTA study, adenocarcinoma was identified as the predominant tumor type 96%. Most patients had received prior chemotherapy (68%) and 72% had brain metastases at baseline.[17,20] The patient characteristics from the ALTA trial and from the Study 101 were similar in their baseline characteristics with no appreciable differences. The patient baseline characteristics from the two trials are outlined in Table 6.4.

Table 6.4. Patient baseline characteristics from clinical trials for patients with ALK-NSCLC with prior crizotinib treatment

	ALTA Trial (Arm B)[1] n = 110	Study 101[17,20] n = 25
Characteristic	180 mg Once Daily (with lead-in)	180 mg Once Daily (with lead-in)

	ALTA Trial (Arm B)[1] n = 110	Study 101[17,20] n = 25
No. of patients	110	25
Median age, years (range)	56.5 (20-81)	57.0 (32-73)
Sex, female No. (%)	64 (58.2)	11 (44.0)
Ethnic Origin No. (%)		
White	76 (69.1)	20 (80.0)
Asian	30 (27.3)	3 (12.0)
Other	4 (3.6)	2 (8.0)
ECOG performance status, No. (%)		
0	45 (40.9)	10 (40.0)
1	56 (50.9)	15 (60.0)
2	9 (8.2)	0
Histology, No. (%)		
Adenocarcinoma	108 (98.2)	24 (96.0)
Adenosquamous	0	1 (4.0)
Squamous	1 (0.9)	0
Large-cell	1 (0.9)	0
Signet cell	0	0
Mucoepidermoid	0	0
Prior chemotherapy, No. (%)	81 (74)	17 (68)
Previous crizotinib treatment, No. (%)	110 (100)	25 (100)
Brain metastases at baseline, No. (%)	74 (67.3)	18 (72.0)

Source: EMA Assessment Report;[6] pCODR submission materials[17]

c) Interventions

ALTA phase 2 trial[1]

In the ALTA trial, patients were randomized to either Arm A (n=112), which received brigatinib 90 mg once daily or Arm B (n=110) in which patients received brigatinib180 mg once daily with a 7-day lead-in period at 90 mg. Treatment continued in the ALTA trial until disease progression, which required the use of alternative systemic therapy, intolerable toxicity or withdrawal of consent. Patients could continue in either Arm after disease progression at the investigator's discretion.[1] As of the February 21, 2017 data-cut off, of the 107 patients from both arms (n=222), 107 patients had progressive disease, with 84 (78.5%) patients continuing brigatinib and 23 (21.5%) discontinuing with OS being better in those that continued therapy (unadjusted hazard ratio (95%CI): 0.32 (0.17-0.62).[93] Dose interruptions and reductions were permitted to manage treatment related AE's based on the judgement of the investigator. All patients in

Arm B received the allocated dosing regimen. The median dose intensity for Arm B was 174 mg per day.[1] As of February 21, 2017 the median dose intensity for Arm B was 169 mg.[18] Palliation and supportive care were permitted during the study for the purpose of management of symptoms and underlying medical conditions.[88]

101 phase 1 / 2 trial[2]

The dosing regimen for the ALTA trial was informed by the Study 101.[2] In the dose escalation phase of the open-label trial, patients received once daily regimens of 30, 60, 90, 120, 180, 240, 300 or 180 mg with a 7-day lead in at 90 mg, or twice-daily regimens of 60, 90 or 120 mg. Specifically, for the ALK-positive NSCLC patients enrolled in the study (n=79), once daily administration was provided at the following doses: 1 patient (1%) received 60 mg, 14 (18%) received 90 mg, 3 (4%) received 120 mg, 23 (29%) received 180 mg once daily, 5 (6%) received 240 mg and finally 28 (35%) received 180 mg with a 7-day lead in at 90 mg, with no patients receiving a 300 mg dose.[2] Alternative dosing schedules were permitted in the study, including twice-daily regimens. Patients continued treatment until disease progression or intolerable toxicity as determined by the investigator. Disease progression was according to RECIST v. 1.1 criteria. Patients could continue in treatment after disease progression, at the investigator's discretion, if they were receiving clinical benefit. Dose interruptions and reductions were permitted in order to manage AE's.[2] Information regarding the median treatment duration or median time on treatment for the 25 patients from Study 101 in this report is not available.

d) Patient Disposition

ALTA phase 2 trial[1]

Of the patients randomized to brigatinib 180 mg once daily with a 7-day lead in period of 90 mg in Arm B (n=110) in the ALTA trial, at the time of the primary data cut-off, 76 patients (69%) in Arm B remained in the study after a median (range) duration of follow-up of 8.3 months (0.1-20.2).[1] By February 21, 2017 with a median (range) of follow-up of 18.6 months (0.1-32.0), 45 patients (41%) remained in study.[12] For the longer term data cut off September 29, 2017, with a median (range) duration of follow-up of 24.3 (0.1-39.2) months, 32 patients (29.1%) remained in the study. The patient disposition for the ALTA study at the September 29, 2017 data cut off is provided in Table 6.5.[6,15,16]

Table 6.5 Patient disposition as of September 29, 2017 (ITT Population)[6]

	Arm A 90 mg QD N=112	Arm B 90 mg QD→ 180 mg QD N=110	Total N=222
Treated patients, n (%)	109 (97.3)	110 (100.0)	219 (98.6)
Treatment ongoing	27 (24.1)	32 (29.1)	59 (26.6)
Treatment discontinued	82 (73.2)	78 (70.9)	160 (72.1)
Primary reason for discontinuation, n (%)			
Documented progressive disease (RECIST v1.1)	54 (48.2)	45 (40.9)	99 (44.6)
Clinical progressive disease	7 (6.3)	11 (10.0)	18 (8.1)
Adverse event	4 (3.6)	12 (10.9)	16 (7.2)
Death	10 (8.9)	1 (0.9)	11 (5.0)
Noncompliance with study drug	0 (0.0)	1 (0.9)	1 (0.5)
Physician decision	3 (2.7)	3 (2.7)	6 (2.7)
Withdrawal by subject	4 (3.6)	5 (4.5)	9 (4.1)
Randomized but never treated, n (%)	3 (2.7)	0 (0.0)	3 (1.4)
Follow-up (months)			
Median	19.56	24.26	22.87
Min, max	0.1, 35.2	0.1, 39.2	0.1, 39.2

Source: EMA Assessment Report[6]

101 phase ½ trial[2]

In Study 101, published by Gettinger et al., 66 patients were recruited during Phase 1 and 71 patients during the expansion phase.[2] Across both phases of the study there were 79 patients with ALK-positive NSCLC with 8 patients being naïve to crizotinib. For the purposes of this pCODR review the patient disposition of the 25 patients (25/79) that had previously received crizotinib and received once daily brigatinib 180 mg with a 7-day lead-in of 90 mg, is of interest. This dosing regimen was only used in the expansion phase of the study. About 60% of patients in the subgroup of 25 patients had discontinued study treatment at the time of the May 31, 2016 data cut. The reason for discontinuation in 44% of patients was documented progressive disease and AEs in approximately 8% of patients.[98]

e) Limitations/Sources of Bias

- The Study 101 was an open label phase 1/2 trial with no active treatment or placebo control groups that was conducted to evaluate the initial safety, tolerability, pharmacokinetics (PK) profile, and preliminary anti-tumor activity of brigatinib in patients with advanced malignancies including NSCLC patients with ALK rearrangements. Therefore, it is difficult to make a conclusion on the efficacy of brigatinib based on the data obtained from this study.

- The analysis of data from the subgroup of 25 patients of interest from Study 101 should be regarded as exploratory as it was not part of the original study protocol and was not presented in the initial clinical trial publication.[2] Within Study 101, patients were not randomized to a specific dosing regimen but were assigned in a step-wise fashion in Phase 2, which could result in allocation bias by the clinicians and research staff.[2]

- The ALTA study is an ongoing phase 2 clinical trial with no active treatment or placebo control groups. Randomized comparisons between the study treatment (brigatinib) and its potential comparators currently available in this setting are needed to justify the observed clinical efficacy and safety outcomes. Although

brigatinib resulted in clinical and survival benefits, no conclusions could be made regarding the efficacy of this drug relative to currently used treatment options for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

In their feedback to the initial recommendation, one of the registered clinicians noted that the sample size of each of the ALTA arms [arm A, n = 112, 90 mg brigatinib once daily; and arm B, n = 110, 180 mg once daily with the 90 mg lead in] is 40-50% larger than the alectinib arm [n = 72] from the phase III ALUR trial; and even ALTA's inferior arm A had a PFS [IRC-assessed PFS 9.2 months (95%CI: 7.4-12.8)] that was better than the best results observed with alectinib in second line [e.g., ALUR trial[39] IRC-assessed PFS 7.1 months (95%CI: 6.3-10.8); or pooled analysis[116] of the alectinib phase II studies (alectinib NP28673 and NP28761) IRC-assessed PFS 8.3 (95%CI: 7.0-11.3)]. It was noted that the larger sample size observed in the ALTA trial would serve to reduce the uncertainty in the efficacy estimates derived from the phase II ALTA trial. In response to the registered clinician's feedback, the pCODR Methods Team noted that notwithstanding a relatively large sample size in the ALTA trial and observed PFS benefit, ALTA was a non-comparative phase II trial and no conclusions can be made regarding the efficacy of this drug relative to currently used treatment options. In addition, it is important to note that the primary objective of phase II (non-randomized or randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase III trials. The purpose of phase II trials is not to provide definitive estimates of efficacy. In order to make a direct comparison between ALK inhibitors, head-to-head RCT data is required, as is currently being conducted in the randomized phase III ALTA 3 trial (NCT03596866)[111].

In their feedback to the initial recommendation, the submitter noted that there is evidence to suggest that the ALK+ NSCLC patient populations enrolled in clinical trials is generalizable to the real-world setting. In two real world studies[112,113] investigating ALK+ NSCLC patient populations, the baseline characteristics, such as age and rates of never-smokers, were very similar to those in the 13 clinical trials enrolling ALK+ NSCLC patients. In addition, brigatinib's phase III, second-line post-crizotinib study (ALTA 3 trial)[111] is currently enrolling patients and the anticipated completion is August 2021. This timing coincides with interim data availability from the CARMA[114]/CARMAC[115] real world studies which will help bring certainty to the results observed in ALTA and ALTA 3 studies in the real-world setting. In response to the submitter's feedback, the pCODR Methods Team noted that, while the real world studies by Hochmair et al. (2018)[112] and Gomet et al (2018)[113] were identified by the pCODR systematic literature search that was conducted as part of the evidence assessment for this submission, they were excluded based on their type of study design; case series or retrospective design, which did not meet the selection criteria of this pCODR review. CARMA[114] is an observational study and CARMAC[115] is a retrospective chart review. Both studies are currently ongoing and no data are currenlty available.

- Due to the open-label design, the study investigators and patients are aware of the treatment status, which may increase the possibility of detection bias and performance bias. Biases associated with the open-label design were partially addressed through the implementation of an IRC, however, this adjudication was

not used as the primary outcome measure for the trials, which relied upon the investigator-assessed efficacy.[1,2] In addition, subjective outcomes (i.e. AEs and QoL) may also be biased as a result of the open-label design.

- Overall survival estimates for the longer-term analyses for both the ALTA Arm B[12] and the Study 101,with median duration of follow-up 24 months, and with 29% of patients remaining in the ALTA trial and less than 40% in the in the Study 101 trial may limit the interpretation of the survival analysis.[20] Overall survival was a secondary outcome in both studies, and without a comparison group as a reference the long term survival should be considered exploratory.

- The number of available patients providing data for the quality of life (QoL) measures (QLQ-C30 scores) collected within the ALTA trial gradually declined[9] with the number of responders declining to 43% (47/110) at cycle 10. Response rates to the QLQ-C30 continued to decline thereafter with data available from 33 patients (30%) at 12 months. The assumption that the QoL beyond 1-year of follow-up is sustained may not be valid.

- The subgroup analyses from the ALTA trial were exploratory in nature as outlined in the clinical trial protocol with a plan to perform within subgroups defined by age, sex, race, geographic region, mutation status, prior anticancer therapies, and other prognostic factors against the primary outcome. As these measures were exploratory they should be interpreted with caution.

- For each of the studies identified, multiple analyses were completed at different time points following the primary evaluation of the trial data, and presented in abstract form following the primary publications of the trials.[1,2] Within the methods sections for the studies, no mention of a longitudinal analysis using data-cuts at different time points was stated, and no statistical adjustment was made for the repeated analysis of outcome measures, rendering these analyses exploratory.

- With respect to the post-hoc analysis of data from the 25 patients from Study 101,[4,5,7] this evaluation was not part of the original study protocol and was not presented in the initial clinical trial publication.[2] Therefore, the analyses are considered exploratory. A full analysis of this patient group, with respect to clinical efficacy and safety, is not available in the public domain. This patient group was comprised of individuals recruited into the expansion phase, of the study.[2] Allocation to receive brigatinib at a dose of 180 mg with a 90 mg lead-in over 7 days was not randomly allocated, and allocation bias may have occurred if individuals were perceived to do better on a particular dose regimen and allocated accordingly.

- For the safety evaluation, it is important to note that since the data come from non-comparative studies, it is difficult to estimate the contribution of the underlying disease on adverse reactions. Furthermore, the safety data provided by the Submitter for the Study 101, includes information on 3 additional patients from the study that were naïve to crizotinib.[17] However, the AEs rates reported with the larger group (N=28) are aligned with the ALTA trial results for the same dosing regimen in Arm B.[1]

- ALTA trial and study 101 is an industry-funded trial in which the staff and representatives of the sponsors were involved in all aspects of conducting the

study including design, data collection, analyses, interpretation, and the preparation of the final manuscript. Thus a potential for conflict of interest exists which could risk the objectivity in the conduct of study as well as the reporting and interpretation of findings.[1,2]

6.3.2.1 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

ALTA phase 2 trial[1]

Primary outcome: Confirmed Objective Response Rate – investigator assessed

For the ALTA trial the primary outcome was investigator-assessed confirmed (ORR) defined as per RECIST v1.1.[1] The objective response rates, at the time of the first study report, were 54% (97.5%CI: 43-65) in patients randomized to receive 180 mg once daily dosing in Arm B.[1] At the time of the February 21, 2017 data cut-off the response was 55%[12] and finally for the last data analysis the confirmed ORR was determined to be 56.4% (97.5%CI: 46.6-65.8) with complete response in 5 (4.5%) patients and partial response occurring in 57 (51.8%).[6,15,16]

Subgroup analysis for confirmed ORR – investigator assessed

Subgroup analysis for confirmed ORR for Arm B was reported by Camidge et al.[89] for the initial data cut off of February 29, 2017. The confirmed ORR for patients with prior chemotherapy was 54% (44/81) and 52% (15/29) for those without prior chemotherapy. For patients with brain metastases at baseline the confirmed ORR was 58% (43/74) and for those without it was 44% (16/36). With respect to the evaluation of race the confirmed ORR for those with an Asian ancestry was 60% (18/30) and for those of non-Asian descent it was 51%(41/80). For patients with best response to prior crizotinib the confirmed response was 64% (47/73) (including patients with partial and complete responses) and was 32% (12/37) for other best responses.[89]

101 phase 1 / 2 trial [2]

For the Study 101 the primary outcome was investigator-assessed objective response rate (ORR) defined as per RECIST v1.1.[2] The ORR for the 25 patients enrolled in Study 101 was 80% (95%CI: 59.3-93.2) with 20 individuals responding to therapy.[6,7] Of these responses to brigatinib, 3 (12%) were classified as complete response to therapy and 17 (68%) were partial responses based on the May 31, 2016 data cut-off.[7]

Secondary outcomes:

ALTA phase 2 trial[1]

Confirmed ORR – assessed by IRC

An independent review committee (IRC) confirmed the investigator-assessed objective response rate. In the ALTA trial (Arm B) 56.4% (95%CI:46.6-65.8) of patients had a confirmed ORR with a complete response in 6 patients (5.5%) and 56 patients (50.9%) having a partial response to treatment at the time of the September 29, 2017 data cut.[6]

101 phase 1 / 2 trial[2] - investigator assessed

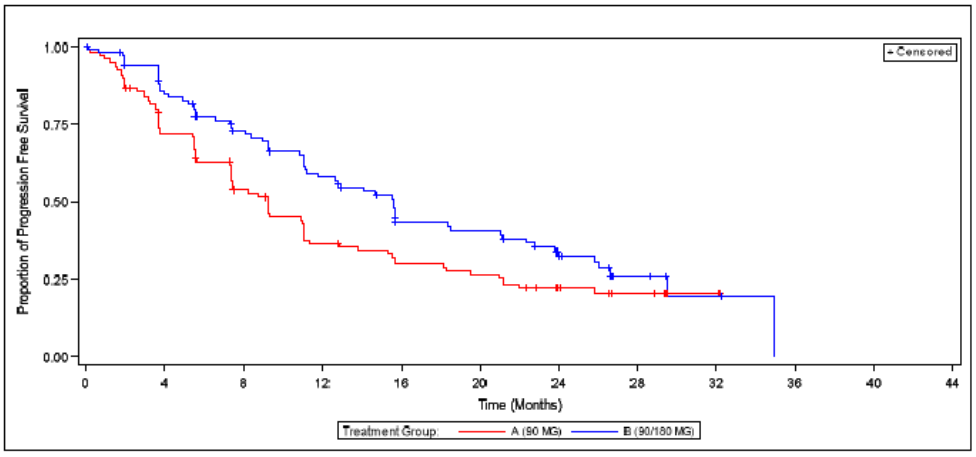
In Study 101 the confirmed ORR for the subgroup of 25 patients was 76% (95%CI: 55-91) with 19 patients responding at both the May 31, 2016 and February 21, 2017 data extraction dates.[7]

Progression free survival (PFS)

ALTA phase 2 trial[1]

In the ALTA trial the investigator assessed PFS in the initial study report for Arm B was 12.9 months (95%CI:11.1-nr).[1] Longer-term estimates determined the PFS to be slightly longer at 15.6 months (95%CI: 11.1-21.0) based on the September 29, 2017 follow-up.[6,16] The investigator assessed PFS by treatment arm for the ITT population in the ALTA trial is presented in Figure 6.2. The IRC PFS similarly for the same analysis was 16.7 months (95%CI: 11.6-21.4). [15,16]

Figure 6.2. Investigator assessed PFS by treatment arm for the ITT population in the ALTA trial[6]



Source: Figure 14.2.1.7.
Abbreviations: ITT, intent to treat; PFS, progression-free survival.
In this analysis, PFS was defined as the time from initiation of treatment until the date at which disease progression was first evident or death, whichever comes first.

Source: EMA Assessment Report[6]

101 phase 1 / 2 trial[2]

The median progression free survival from Study 101 for the 25 patients as of the latest cut-off date of February 21, 2017 was 16.3 months (95%CI: 9.2-28.1).[7] The estimated probability of PFS was 62% (95%CI: 40-78).[7]

Overall survival (OS)

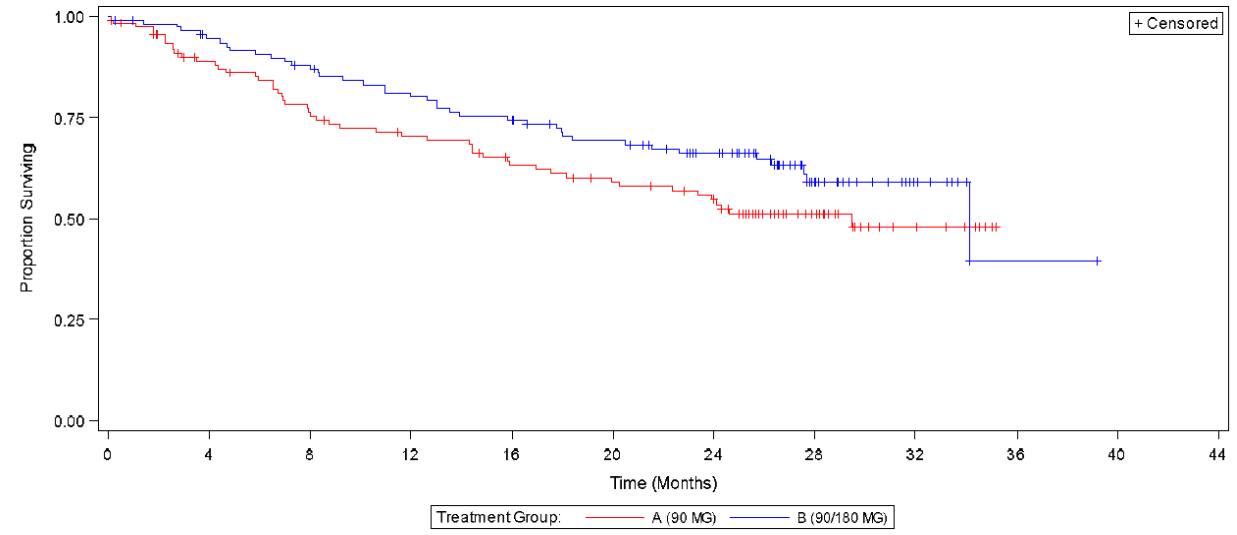
ALTA phase 2 trial[1]

For patients in Arm B of the ALTA trial, the 1-year probability of survival was 80.1% (95%CI: 71-87) based on the September 29, 2017 data extraction and the 2-year probability of survival was determined to be 66% (95%CI: 56-74).[15,16] The median OS

for Arm B was 34.1 months (95%CI: 27.7-nr) with 40 events (36.4%) in the 110 patients.[6]

The OS is presented in Figure 6.3 by treatment arm for the ITT population from the ALTA trial as of September 29, 2017.

Figure 6.3. OS by Treatment Arm (ITT Population)[6]



Source: EMA Assessment Report[6]

101 phase 1 / 2 trial[2]

The 1-year OS probability for the subgroup of 25 patients, based on a data cut-off date of February 21, 2017, was estimated to be 84% (95%CI: 63-94) with a median OS (95%CI) of 29.5 months (95%CI:21.4-nr). The 2 year overall survival probability was 64% (95%CI:42-79).[7]

Duration of Response (DOR)

ALTA phase 2 trial[1]

The median DOR for those patients treated in the ALTA trial was 13.8 months (95% CI: 10.2-19.3) in Arm B at the time of the September 29, 2017 analysis as determine by the investigator.[6,16] Further analysis by the IRC, within the ALTA trial, determined that the median duration of response to be slightly longer at 15.7 months (95%CI: 12.8-21.8) based on the September 29, 2017 data cut-off.[6]

101 phase 1 / 2 trial[2]

Similarly, in the Study 101 trial, for the subgroup of 25 patients, the median duration of response was 14.9 months (95%CI: 7.9-33.3) up to the data cut of February 21, 2017.[6]

Disease Control Rate (DCR)

ALTA phase 2 trial[1]

Disease control rates were reported in the ALTA Trial for Arm B. The rate was 86% (95%CI: 79-92) in 95 patients, as reported in the original publication by Kim et al.

at the time of the initial data cut-off of February 29, 2016.[1] Similarly, for the IRC assessed rates, the DCR was 84% (95%CI: 75-90) in 92 patients for Arm B.[1]

Exploratory Subgroup Analyses of Patients with Brain Metastases

An exploratory study by Camidge et al. was completed using data from both Study 101[2] and the ALTA study[1] in patients with asymptomatic brain metastases at baseline.[3] In Study 101, patients with brain metastases were originally excluded however, based on intracranial activity a protocol amendment was approved to include this patient population.[3] Neurologically stable patients with brain metastases without the need for increasing doses of corticosteroids or anticonvulsants were included. Active brain metastases were defined as those without prior radiotherapy or with investigator assessed progression after radiotherapy. Central nervous system (CNS) lesions greater than or equal to 10 mm were considered measurable.[3] In the ALTA trial, patients were excluded if they had symptomatic CNS metastases that required an increasing dose of corticosteroids or were neurologically unstable. Intracranial response in patients with one or more lesions using criteria based on RECIST as a greater than or equal to a 30% decrease in the sum of the longest diameters of the target lesions and non-progression in non-target lesions.[3] In the following results for the ALTA trial are reported, as outcomes for the subgroup of 25 patients from Study 101, were not reported in Camidge et al.[3]

ALTA phase 2 trial

The evaluation of the efficacy and safety in patients with brain metastases at baseline was completed in the ALTA trial at various follow-up intervals.[1,3,12-14] The primary paper outlining these results was recently published by Camidge et al in 2018.[3]

The results of the exploratory subgroup analyses show that the benefit of brigatinib was consistent across all subgroups with brain metastases at baseline.

Objective Cranial Response Rate (OCRR)

The analysis of the confirmed OCRR as determined by the IRC in both studies was stratified according to measurable and non-measurable brain metastases at baseline. For patients enrolled into the ALTA trial (Arm B), 18 patients had measurable brain metastases. For these patients the confirmed OCRR was 66.7% (95%CI: 41.0-86.7) with no patients having a complete response.[1] This rate remained constant across all analysis time points up to September 29, 2017.[6] Results from the study for those patients with only non-measurable brain metastases (N=55) in Arm B, showed that the confirmed OCRR was 18% (95%CI: 9-31) with 10 patients (18%) having a cranial complete response[3] and again remained constant across all analysis time points up to September 29, 2017.[6]

Progression Free Survival

For those individuals with brain metastases at baseline in Arm B (n=73) of the ALTA trial, the median whole body PFS was 12.9 months (95%CI: 9.3-nr) at the May 31, 2016 data extract.[3]

Overall Survival

For those patients with brain metastases at baseline in Arm B (n=73), the probability of survival was 85% (95%CI: 73-92) at the May 31, 2016 data extraction.[3]

Disease Control Rate (DCR)

For those individuals within the ALTA trial with brain metastases at baseline (N=73) and enrolled in Arm B in the trial, the DCR was 86.3% (95%CI: 76.2-93.2) in 63 individuals as reported at the time of the May 31, 2016 data cut-off date.[3]

Intracranial Progression Free Survival (IPFS)

The IPFS for the study was defined as the time from first dose to progression in brain or death, which ever occurred first.[3] The IRC median IPFS for the Arm B patients with any asymptomatic brain metastases at baseline was reported as 12.8 months (11.0-nr) in the primary study report.[1] The median IPFS was 18.4 months (95%CI: 12.6-23.9) from the September 29, 2017 data-cut evaluations.[16]

Intracranial Disease Control Rate (IDCR)

When examining the results from the ALTA trial, in patients in Arm B the IDCR was 83% (95%CI: 59-96) in 15/18 patients with measureable brain metastases at baseline.[1,3,12] Another estimate for IDCR was available for non-measurable metastases (n = 55) at the September 29, 2017 data cut: IDCR was 85% (95%CI: 73-94).[6]

Duration of Intracranial Response (DOIR)

The intracranial duration of response for the exploratory study was defined as the time from first intracranial response to progression.[3] The median duration of intracranial response from the ALTA trial in Arm B in those with measurable brain metastases (n = 18) was 16.6 months (95%CI: 3.7-nr) as of the September 29, 2017 data cut off.[6,16]

Harms Outcomes in Patients with Brain Metastases at Baseline

In the ALTA trial, Arm B, in those individuals with brain metastases at baseline all patients experienced at least one adverse event (AE). Of these AEs, 36 patients (49%) had a Grade 3 severity or greater AE with serious TEAE occurring in 38% of patients. Treatment doses of brigatinib were reduced in 18% of patients and 38% had a dose interruption related to a TEAE. Therapy was discontinued in 10% (7 patients) secondary to a TEAE.[3]

Health Related Quality of Life

ALTA phase 2 trial[1]

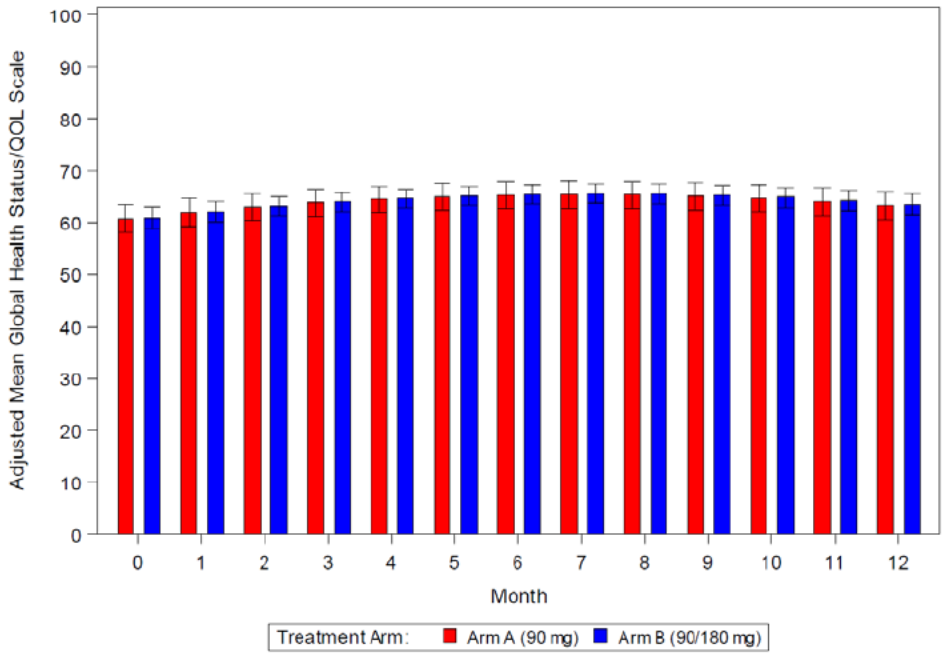
Health related quality of life was assessed in the ALTA trial[1,10] using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-30). Baseline mean (SD) assessments for the EORTC-QLQ-30 were 58.49 (23.40), for the patients randomized to 180 mg once-daily a score, where the scale is 1-100, with 100 as the highest score. As reported in the supplement of the main trial publication by Kim et al.[10] the observed scores were comparable to reference values for the QLQ-C30 for Stage III-IV lung cancer based on data provided by EORTC qualify of Life Group Members and other users of the QLQ-C30. HRQoL was measured monthly, increased up to 7 months following initiation of therapy and then declined. However, the mean values remained above the baseline mean although there were increasingly fewer patients with less than 50% of the patients providing QLQ-C30 scores at cycle 10 and beyond.[1,9,10] In an evaluation of the ALTA trial, presented as an abstract form,[92] assessing patient reported outcomes data from baseline to cycle 5, 80% of all patients QLQ-C30 scores improved or showed no change from baseline at cycle 5 (5 months on

treatment) with 50% experiencing a clinically meaningful improvement.[92] Multivariable mixed effects models were employed to assess adjusted mean changes from baseline. The numerical value of a clinically meaningful improvement was not reported in the abstract. However, in a separate evaluation of the data from the ALTA trial, with the purpose to assess the clinically meaningful change of the EORTC QLQ-C30 in patients with NSCLC, a clinically meaningful change, demonstrating HRQoL benefit, was determined as a changed of 8.33 points from baseline at cycle 3.[94]

The number of patients providing QLQ-C30 scores declined to 43% (47/110) at cycle 10 with an EORTC-QLQ-30 mean score (SD) of 68.97 (22.43) and continued to decline thereafter with data available from 33 patients (30%) at 12 months and with a maximal QLQ-C30 follow-up to cycle 21 (n=2).[9] The reduction in the number of respondents leads to uncertainty in the quality of life results beyond 1 year and possibly in earlier cycles. HRQol estimates up to cycle 12 or earlier may not represent an accurate picture of the patients' experiences with brigatinib for a longer period of time. The last assessment was completed 30 days after the last study dose was administered. Therefore HRQoL in the post-progression period remains largely unknown. Additionally, the trial was non-randomized and the impact of brigatinib on patient's QoL in relation to other therapies is unknown. In order to obtain utility values of the economic model provided in this submission, scores from the EORTC-QLQ-30 were mapped to the European Quality of Life Five Dimensions scale (EQ-5D), baseline utility scores were calculated to be 0.67 for Arm B.[91] Utility scores improved through 5 months to 0.78 in the Arm B, 180 mg once daily group.[91]

The quality of life measurements over the course of the first 12 months of the ALTA trial are presented in Figure 6.4.[10]

Figure 6.4 Quality of Life Measures using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-30) over 12 months in the ALTA trial.[10]



Source: Source: EMA Assessment Report[6]

Health related quality of life measures were not collected within the Study 101.

Harms Outcomes

Data related to adverse events were made available from the Submitter as of the February 21, 2017 data cut off for both studies.

ALTA phase 2 trial[1]

In the ALTA trial, Arm B, all patients experienced at least one adverse event (AE). Seventytwo patients (65.5%) had a Grade 3 severity or greater AE with serious treatment-emergent adverse events (TEAE) occurring in 50.9% of patients. Twenty patients (18.2%) experienced a serious treatment related TEAE. Treatment doses of brigatinib were reduced in 30% of patients and 59.1% had a dose interruption related to a TEAE. Therapy was discontinued in 10.9% (12 patients) secondary to a TEAE.[17]

101 phase 1 / 2 trial[2]

From Study 101, data related to all ALK-positive NSCLC patients receiving brigatinib according to the Health Canada approved label, independent of their prior crizotinib utilization (N=28) was provided by the Submitter. Of this group 96.4% (n=27) experienced at least 1 TEAE. Of these AEs 20 patients (71.4%) had a Grade 3 severity or greater AE with serious treatment-emergent adverse events (TEAE) occurring in 42.9% of patients. Three patients (10.7%) experienced a serious treatment related TEAE. Treatment doses of brigatinib were reduced in 21.4% of patients and 53.6% had a dose interruption related to a TEAE. Therapy was discontinued in 10.7% (3 patients) secondary to a TEAE.[17]

An overall summary of the adverse event rates for the ALTA trial and Study 101 are presented in Table 6.6.[17]

Table 6.6 Summary of Adverse Events in the Study 101 and ALTA trial in the expansion phase doses and All Patients in Patients with ALK-positive NSCLC.[17]

	AP26113-11-101			AP26113-13-201 [1]			
	90 QD ALK+ NSCLC (N = 14)	90 to 180 QD ALK+ NSCLC (N = 28)	All Patients [2] (N = 137)	90 QD (N = 109)	90 to 180 QD (N = 110)	All Patients (N = 219)	Pooled Total (N = 356)
Any TEAE	14 (100 0)	27 (96 4)	136 (99 3)	109 (100 0)	110 (100 0)	219 (100 0)	355 (99 7)
Treatment-Related TEAE	13 (92 9)	27 (96 4)	126 (92 0)	87 (79 8)	105 (95 5)	192 (87 7)	318 (89 3)
Serious TEAE	7 (50 0)	12 (42 9)	72 (52 6)	52 (47 7)	56 (50 9)	108 (49 3)	180 (50 6)
Serious Treatment-Related TEAE	2 (14 3)	3 (10 7)	24 (17 5)	8 (7 3)	20 (18 2)	28 (12 8)	52 (14 6)
Grade 3-5 TEAE	8 (57 1)	20 (71 4)	97 (70 8)	64 (58 7)	72 (65 5)	136 (62 1)	233 (65 4)
Grade 3-5 Treatment-Related TEAE	5 (35 7)	18 (64 3)	59 (43 1)	24 (22 0)	47 (42 7)	71 (32 4)	130 (36 5)
Grade 3-5 Serious TEAE	6 (42 9)	11 (39 3)	64 (46 7)	42 (38 5)	46 (41 8)	88 (40 2)	152 (42 7)
Grade 3-5 Serious Treatment-Related TEAE	2 (14 3)	3 (10 7)	20 (14 6)	6 (5 5)	13 (11 8)	19 (8 7)	39 (11 0)
TEAEs Leading to Treatment Discontinuation [3], Dose Reduction, or Dose Interruption	6 (42 9)	17 (60 7)	75 (54 7)	45 (41 3)	71 (64 5)	116 (53 0)	191 (53 7)
TEAEs Leading to Treatment Discontinuation [3]	0	3 (10 7)	14 (10 2)	4 (3 7)	12 (10 9)	16 (7 3)	30 (8 4)
TEAEs Leading to Dose Reduction	0	6 (21 4)	18 (13 1)	10 (9 2)	33 (30 0)	43 (19 6)	61 (17 1)
TEAEs Leading to Dose Interruption	6 (42 9)	15 (53 6)	68 (49 6)	44 (40 4)	65 (59 1)	109 (49 8)	177 (49 7)

(Database Cutoff Date: 2017-02-21) Executed: 05JUN2017 10:19
[1] Patients enrolled in study AP26113-13-201 were ALK+ NSCLC per entry criteria
[2] 'All Patients' represents the total Safety Population from study AP26113-11-101 consistent with table definition
[3] Does not include patients who had an AE action of 'Drug Withdrawn' and a primary reason for treatment discontinuation of 'Progressive Disease'
P \Medical\Biostatistics\AP26113\Module_2_2016\2017-02-21\Dev\TLF\T_14_3_1_1_1_AE_Summary_by_Two_Column_Groups_Study_Doses_Treated sas

Source: pCODR Submission Materials[17]

Treatment Emergent Adverse Events (TEAEs)

ALTA phase 2 trial[1]

In the ALTA trial, the most common TEAEs in Arm B were nausea (40%), diarrhea (38%), cough (34%),and headache (27%). Grade 3 or greater TEAE were reported in a poster by Huber et al. using data from the September 29, 2018 data cut.[15,16] In Arm B of the ALTA trial, based on this latest data analysis, the following grade 3 or greater TEAE occurred (in ≥3% of patients): increased blood creatine phosphokinase (13%), hypertension (5%), increased lipase (5%), rash (4%), pneumonitis (4%), increased aspartate aminotransferase (4%), increased aspartate aminotransferase (3%), hyponatremia (3%), nausea (1%), and increased amylase (2%).[15,16]

101 phase 1 / 2 trial[2]

Within the 28 patients from Study 101, the most commonly reported TEAE were nausea (50%), diarrhea (50%), headache (46%), fatigue (43%), arthralgia (36%), cough (43%), back pain (36%),upper respiratory tract infections (32.1%), decreased appetite (29%), hypertension (29%) and dyspnoea (25%).[17]

Serious Adverse Events

ALTA phase 2 trial[1]

In the ALTA trial 14 (6%) participants experienced early onset pulmonary adverse events (including dyspnea, hypoxia, cough, pneumonia, or pneumonitis) while receiving 90 mg once daily of brigatinib. One patient continued treatment, six resumed treatment, and seven discontinued.[1] Seven patients (3%) had grade 3 events. The early onset pulmonary adverse events occurred within a median time of two days upon initiation of therapy with a range of 1 to 9 days.[1] These events occurred in both arms (A +B) while on 90 mg once daily. No such AEs were observed once patients in arm B were moved to the 180 mg daily dose.

101 phase 1 / 2 trial[2]

Not reported for the subgroup of 25 patients.

Treatment-Emergent AE leading to Death

For patients treated with a dose of 180 mg daily with a 7-day lead-in, AEs leading to death within 30 days of the last dose or related to the study drug were reported for both studies together (ALTA trial [Arm B; N = 110] and Study 101 [N = 25]); 12 patients (8.7%) out of 138 experienced at least one of these AEs. The causes of these AEs were listed as: neoplasm progression in 8 (5.8%) patients, and pneumonia, sudden death, hydrocephalus, and urosepsis in one patient (0.7%) each.[17]

6.4 Ongoing Trials

The pCODR systematic review identified one on-going trial. The details of the trial are presented in Table 1.

Table 1: Ongoing trial of brigatinib in anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic NSCLC, who have progressed on or who were intolerant to crizotinib.[111]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study name ALTA 3[111] A Phase 3 Randomized Open-label Study of Brigatinib (Alunbrig®) Versus Alectinib (Alecensa®) in Advanced Anaplastic Lymphoma Kinase-Positive Non Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (Xalkori®) ClinicalTrials.gov: NCT03596866 **Characteristics** Open-label, Phase 3, Randomized Controlled Trial. **Estimated Sample size** N = 246 **Locations** Canada, United States **Patient Enrolment Dates** Recruiting **Estimated Primary Completion** Date: September 4, 2023 **Funding** Takeda (Ariad Pharmaceuticals)	Key Inclusion Criteria: • ECOG performance status of 0 to 2. • Histologically or cytologically confirmed stage IIIB (locally advanced or recurrent) or stage IV non-small cell lung cancer (NSCLC). • Must meet one of the following criteria: o Have documentation of ALK rearrangement by a positive result from the Vysis ALK Break-Apart fluorescence in situ hybridization probe Kit or the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx. o Have documented ALK rearrangement by a different test and be able to provide tumor sample to the central laboratory. • Progressive disease (PD) while on crizotinib, as assessed by the investigator or treating physician. • Treatment with crizotinib for at least 4 weeks before progression. • Received no other ALK inhibitor other than crizotinib. • No more than 2 prior regimens of systemic anticancer therapy in the locally advanced or metastatic	Intervention: Brigatinib 180 mg orally once daily with a 7-day lead-in at 90 mg. Comparator: Alectinib 600 mg orally twice daily	Primary: PFS Secondary: OS ORR TTR DOR DOIR OCRR IPFS HRQoL HRQoL-LC

	setting. Note: a systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic agent used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this neoadjuvant or adjuvant therapy. • At least 1 measurable (ie, target) lesion per response evaluation criteria in solid tumors (RECIST) v1.1. • Recovered from toxicities related to prior anticancer therapy to national cancer institute common terminology criteria for adverse events (NCI CTCAE) v4.03 grade ≤1. • Adequate organ function, as determined by: o Total bilirubin ≤1.5 times the upper limit of normal (ULN). o Estimated glomerular filtration rate ≥30 mL/minute/1.73 m2, using the modification of diet in renal disease equation. o Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 × ULN; ≤5 × ULN is acceptable if liver metastases are present. o Serum lipase ≤1.5 × ULN. o Platelet count ≥75 ×109/L. o Hemoglobin ≥9 g/dL. o Absolute neutrophil count ≥1.5 × 109/L. • Suitable venous access for study-required blood sampling (ie, including PK and laboratory safety tests) <u>Key Exclusion Criteria:</u> • Participated in the control (crizotinib) arm of Study AP26113-13-301 (ALTA 1L). • Received crizotinib within 7 days of randomization. • A history or presence at baseline of pulmonary interstitial disease, drug related pneumonitis, or radiation pneumonitis. • Uncontrolled hypertension. Participants with hypertension should be under treatment for control of blood pressure upon study entry. • Received systemic treatment with strong cytochrome P-450 (CYP) 3A inhibitors, strong CYP3A inducers, or moderate CYP3A inducers within 14 days before randomization. • Treatment with any investigational systemic anticancer agents within 14		

	days or 5 half-lives, whichever is longer, before randomization. • Received chemotherapy or radiation therapy within 14 days of randomization except for stereotactic radiosurgery (SRS) or stereotactic body radiation therapy. • Received antineoplastic monoclonal antibodies within 30 days of randomization. • Major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed. • Symptomatic CNS metastases (parenchymal or leptomeningeal) at screening (participants with asymptomatic brain metastases or participants who have stable symptoms and did not require an increased dose of corticosteroids to control symptoms within 7 days before randomization will be enrolled). • Current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Participants with leptomeningeal disease and without cord compression are allowed. • Significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to the following: o Myocardial infarction within 6 months before randomization. o Unstable angina within 6 months before randomization. o New York Heart Association Class III or IV heart failure within 6 months before randomization. o History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician. o Any history of clinically significant ventricular arrhythmia. • Cerebrovascular accident or transient ischemic attack within 6 months before first dose of study drug. • Malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug. • Ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics. • Known history of HIV infection. Testing is not required in the absence of history. • Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.		

	• Known or suspected hypersensitivity to brigatinib or alectinib or their excipients. • Life-threatening illness unrelated to cancer.		

Abbreviations: **ALK**=anaplastic lymphoma kinase; **CNS**=Central nervous system; **DOIR** = duration of intracranial response; **DOR=**duration of response; **ECOG**=Eastern Cooperative Oncology Group; **HIV**=Human immunodeficiency viruses; **HRQoL**=Health related quality of life; **HRQoL-LC**=Health related quality of life-Lung Cancer; **IDOR**=intracranial duration of response; **IPFS**=Intracranial progression free survival; **OCRR**=overall cranial response rate; **ORR**=overall response rate; **PD**=Progressive disease; **PFS**=Progression free survival; **TTR**=Time to response.

Data Source: Clinicaltrials.gov[111]

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of brigatinib:

- Critical appraisal of the Manufacturer's submitted indirect treatment comparisons (ITCs), including naïve comparisons, unanchored matching-adjusted indirect treatment comparisons (MAICs), and a network meta-analysis (NMA) comparing brigatinib to alectinib, ceritinib, crizotinib retreatment, chemotherapy, and best supportive care in patients with ALK+ NSCLC who have been previously treated with crizotinib.

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

The CGP noted that the submitter-provided indirect treatment comparisons (ITCs) included 're-treatment with crizotinib' as a comparator. This comparator was not included in the economic model and the CGP did not consider 're-treatment with crizotinib' an appropriate comparator as it is not funded for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. The CGP noted that clinicians would not retreat with crizotinib in the present setting.

7.1 Critical Appraisal of the Manufacturer's Submitted ITCs

7.1.1 Objective

There are no randomized trials that directly compare the efficacy of brigatinib as second-line therapy to other available tyrosine kinase inhibitors, including ceritinib and alectinib, in patients who have previously received crizotinib. Therefore, the Manufacturer conducted ITCs, including naïve comparisons, unanchored MAICs, and NMAs to examine the comparative efficacy and safety of tyrosine kinase inhibitors for ALK+ NSCLC in patients who previously received crizotinib.[20] The objective of this section is to summarize and critically appraise the methods and results of the performed analyses, which compared brigatinib to crizotinib retreatment, alectinib, ceritinib, chemotherapy, and best supportive care in terms of efficacy, safety, and tolerability as a second-line treatment post-crizotinib.

7.1.2 Findings

Objective

The objective of the Manufacturer-submitted ITC report was to "…assess the safety, tolerability, and efficacy of brigatinib compared with other pharmacological treatments for patients with ALK+ NSCLC (ceritinib, alectinib, crizotinib retreatment, chemotherapy) in the post-crizotinib setting."[20]

Systematic Literature Review

A systematic literature review (SLR) was conducted to identify relevant literature for the ITC.[97] The SLR involved two stages; the first stage evaluated brigatinib, alectinib, crizotinib retreatment, ceritinib, and best supportive care (BSC), and the second stage included chemotherapy with pemetrexed (with or without cisplatin) or docetaxel as a treatment alternative. The objectives of the SLR were to:

- "Identify reports of the efficacy and safety and tolerability of post-crizotinib treatments (brigatinib, ceritinib, crizotinib, alectinib, and best supportive care) for ALK+ NSCLC – Stage I only

- Identify reports of the efficacy and safety and tolerability of post-crizotinib treatments (pemetrexed [with or without cisplatin] and docetaxel) for ALK+ NSCLC – Stage 2 only
- Assess the feasibility of indirect treatment comparison of relevant reports
- Present and describe outcome data reported in studies of post-crizotinib treatments for ALK+ NSCLC."[97]

Studies that were eligible for inclusion in the SLR evaluated adults (≥ 18 years) with ALK+ NSCLC and no other co-mutation who had received previous treatment with crizotinib.[97] Eligible interventions for Stage 1 of the SLR included monotherapy or combination therapy with alectinib, best supportive care, brigatinib, ceritinib, and crizotinib, and Stage 2 included studies evaluating docetaxel or pemetrexed (with or without cisplatin).[97] Studies could be of any duration and length of follow up, and could be experimental (randomized controlled trials, randomized non-comparator studies, non-randomized studies, open-label extension studies), or observational designs.[97] Systematic reviews with or without meta-analyses and conference proceedings were also eligible for inclusion. The outcomes of interest included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), time to response (TTR), patient-reported outcomes (PROs), and adverse events and safety assessments.[97]

The report authors searched a number of databases (Medline, Embase, Pubmed, Cochrane Database of Systematic Reviews, Cochrane Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and the Cochrane Library Health Technology Assessment database), clinical trials registries (clinicaltrials.gov, International Clinical Trials Registry Platform, European Union Clinical Trials Register, and PharmNet.Bund), relevant conference websites, and Web of Science to identify relevant studies.[97] Study selection was conducted by two independent reviewers, whereas data extraction and quality assessment (using the Cochrane Risk of Bias tool) was conducted by one reviewer and checked by another.[97]

Systematic Review Results

The initial search was conducted on August 2, 2017, with a subsequent search update completed on November 14, 2017.[97] A total of 34 relevant publications were identified and selected for inclusion from the Stage 1 search: 25 studies reported data from 7 clinical trials, and 9 studies were observational designs. Three relevant publications were identified from the Stage 2 search, however, these three studies were already identified in the Stage 1 search.[97] Full PRISMA diagrams were provided for each step of the study review process, and a list of excluded studies based on full-text review was provided in the report for each Stage.[97]

Of the seven included clinical trials, two evaluated brigatinib (ALTA and Study 101),[2,11,56] two evaluated ceritinib (ASCEND-2 and ASCEND-5),[99,100] and three studies evaluated alectinib (ALUR, NP28673, and NP28761).[101-103] Of note, information that was identified for the ALUR trial was limited to a conference abstract and the associated conference presentation because the full results of the ALUR trial were not published until June 2018.[39,101,104] As a result, the details regarding the ALUR trial in the SLR report and ITC report were limited to the information available in the conference proceedings.[20,97] There were no clinical trials identified evaluating best supportive care or crizotinib in people who had previously received crizotinib.

Nine observational studies were identified in the SLR, however, three studies that evaluated alectinib and two studies that evaluated ceritinib were excluded because higher-quality clinical trials were available to provide data for these agents in the

analyses. As a result, only four observational studies were reported, and these studies provided data for crizotinib and best supportive care.[105-108] However, only three of the observational studies were included in the ITC report: the publication by Kayaniyil et al (2016) was not included, and no rationale was provided as to why this study was not used in the ITC.[20]

Study Quality

The open-label nature of all of the included clinical studies increased the risk for performance bias and detection bias, and only the ASCEND-5 study attempted to minimize the likelihood of detection bias through efficacy outcome assessment by a blinded independent review committee.[100] While NP28673 and NP28761 utilized independent review committees to assess efficacy outcomes, since these were single-arm studies, blinding was not possible.[102,103] All other included clinical studies used investigator assessment to evaluate the development of efficacy outcomes, increasing the risk for detection bias.[1,2,99,101,104] Five of the seven studies had no control group, minimizing the comparative applicability of the results.[1,2,99,102,103] The likelihood of selective reporting was reported as low for all studies except the ALUR study, which was not fully published at the time the SLR was created, therefore data for the ALUR study was available from a conference abstract and a conference oral presentation only.[101,104] NP28673 did not report participant attrition due to discontinuation, and NP28703 did not report reasons for discontinuation, limiting the ability to assess the possibility of attrition bias in these studies.[102,103]

A quality assessment was not reported in the SLR for the included observational studies.[97]

Feasibility of Indirect Treatment Comparisons

While one of the objectives of the SLR was to "Assess the feasibility of indirect treatment comparison of relevant reports", no details were provided as to how feasibility was to be assessed, and there was no evaluation of this objective in the SLR.[97]

The major feasibility assumption relating to unanchored MAICs is that the study (or studies) providing the individual patient data (IPD) and the studies providing comparator summary data include all prognostic factors and effect modifiers.[109] This assumption must be met to ensure the results from the unanchored MAIC are unbiased.[109] While the NICE DSU TSD 18 provides methods for estimating residual bias associated with unexplained heterogeneity between outcomes, this assessment was not provided in the ITC Report.[20,109]

An important feasibility assumption relating to conducting NMAs is that the included studies form a connected network based on head-to-head studies or indirect comparisons through a common comparator.[21] As discussed in the ISPOR-AMCP-NPC Good Practice Task Force Report, "If some interventions of interest are not part of the same network, then it is not possible to perform an indirect comparison of treatment effects of these interventions without a substantial risk of bias…"[21] Given that the included brigatinib studies did not have a comparator arm, it is not possible to create a network and conduct an NMA with the identified comparator studies without resulting in substantial bias associated with the results.

Other considerations for feasibility for ITCs include whether study inclusion and exclusion criteria were similar across included studies, whether covariates and outcomes were measured in the same way in all included studies (such as with the same diagnostic criteria, over the same time periods of assessment), and whether there was selective reporting of outcomes in the included studies.[21]

Table 7.1 provides details regarding the clinical trials and observational studies that were included in the ITC analyses. Table 7.2 provides the patient characteristics for each study.

Table 7.1. Details of the Included Clinical Trials and Observational Studies[17,20,97]

Study	ALTA	Study 101	ASCEND-5	ASCEND-2	ALUR	NP28673	NP28761	Ou	Hong	Duruisseaux
Study Design	Randomized open-label	Non-RCT open-label	RCT open-label	Single-arm clinical trial	RCT open-label	Single-arm clinical trial	Single-arm clinical trial	Observational follow up of single-arm clinical trials PROFILE 1001/1005	Observational	Observational
Intervention	Brigatinib 90mg Brigatinib 180mg	Brigatinib 90mg Brigatinib 180mg	Ceritinib	Ceritinib	Alectinib	Alectinib	Alectinib	Crizotinib beyond progressive disease (CBPD)	CBPD	Best Supportive Care
Comparator	No comparator	No comparator	Chemotherapy: pemetrexed or docetaxel	No comparator	Chemotherapy: pemetrexed or docetaxel	No comparator	No comparator	Discontinuation of crizotinib at progressive disease	No comparator	No comparator
N patients	222	13* 25*	231	140	107	139	87	CBPD: 120 No crizotinib: 74	33	105
Phase	2	1/2	3	2	3	2	2	PROFILE 1001: 1 PROFILE 1005: 2	Not applicable	Not applicable
Location and setting	71 cancer centres (USA n =15; Canada n =1; Europe n =38; Australia n = 6; Asia n = 11)	9 cancer centres in USA and Spain	110 sites across USA, Belgium, Canada, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Republic of Korea, Lebanon, Netherlands, Portugal, Russian Federation, Singapore, Spain, Switzerland, Turkey, UK	51 global sites across Canada, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Netherlands, Singapore, Spain, United Kingdom, United States	54 study locations across Belgium, Bulgaria, France, Germany, Hong Kong, Hungary, Italy, Republic of Korea, Norway, Poland, Portugal, Russia, Slovakia, Spain, Turkey	56 centres in 16 countries (Australia, Belgium, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Russia, Singapore, South Korea, Spain, Sweden, Taiwan, UK, USA	28 centres in USA and Canada	PROFILE 1001: 36 centres in USA, Australia, Japan, and South Korea PROFILE 1005: 143 centers in USA, Australia, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hungary, Ireland, Italy, Japan, South Korea, Netherlands, Poland, Russian Federation, Spain, Sweden, Taiwan, and	Sun Yat-Sen University Cancer Center, Guangzhou, China	France: data from the French Crizotinib Expanded Access Program database and 80 participating centres

Study	ALTA	Study 101	ASCEND-5	ASCEND-2	ALUR	NP28673	NP28761	Ou	Hong	Duruisseaux
								United Kingdom		
Treatment duration	Until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Treatment in either arm could be continued at the investigator's discretion after progression.	Until disease progression or intolerable toxicity.	Until disease progression or adverse events detrimental to patient's wellbeing, laboratory abnormalities, pregnancy, unplanned deviations from the prescribed dose or use of prohibited treatments. Treatment was also discontinued if an adverse event or laboratory abnormality met the prespecified discontinuation criteria detailed in the study protocol. Treatment could also be discontinued because of a patient or guardian decision, loss to follow-up, and death. Treatment could be continued for clinical benefit beyond disease progression.	Until radiologically documented disease progression by investigator (RECIST, version 1.1), unacceptable toxicity, or withdrawal of consent. Treatment beyond progression was permitted in patients who were still experiencing clinical benefit.	Until progression, death or withdrawal. Treatment could be continued for clinical benefit beyond disease progression.	Until disease progression, unacceptable toxicity, or withdrawal of consent occurred. Treatment beyond disease progression was permitted if the treating physician considered it beneficial in consultation with the sponsor.	Until disease progression, withdrawal, or death. Treatment beyond progression was allowed if there was reasonable evidence of ongoing clinical benefit in the opinion of the treating investigator	Not applicable	Not applicable	Not applicable
Median duration of follow up (range)	May 2016 data cut: 7.8 months (0.1 -16.7) 8.3 months (0.1 to 20.2) February 2017 data cut: 16.8 months 18.6 months	NR for eligible subgroup **	16.6 months (IQR 11.6-21.4) 16.4 months (IQR11.4-21.4)	11.3 months (0.1-18.9)	6.5 months 5.8 months	Primary data cut off 30.0 weeks (2.0-53.0) Updated data cut off 47.0 weeks (2.0-73.0)	Primary analysis: 4.88 months (1.1-13.6) Updated analysis: 9.9 months (1.1-19.9) Extended analysis: 17.0 months (1.1-28.6)	25.2 weeks (3.7 - 115.9)	17.6 months (8.0 - 46.1)	44.4 months (95% CI: 40.6 - 47.5)

Study	ALTA	Study 101	ASCEND-5	ASCEND-2	ALUR	NP28673	NP28761	Ou	Hong	Duruisseaux
Dosing regimen	Oral brigatinib 90mg once daily Oral brigatinib 180mg once daily with 7-day lead in of 90mg once daily	Oral brigatinib 90mg once daily Oral brigatinib 180mg once daily with 7-day lead in of 90mg once daily	Oral ceritinib 750mg daily Intravenous Chemotherapy pemetrexed 500mg/m2 or docetaxel 75mg/m2 every 21 days	Oral ceritinib 750mg daily Intravenous Chemotherapy pemetrexed 500mg/m2 or docetaxel 75mg/m2 every 21 days	Oral alectinib 600mg twice daily	Oral alectinib 600mg twice daily	Oral alectinib 600mg twice daily	Oral crizotinib 250mg twice daily with modifications as necessary	Oral crizotinib 250mg twice daily with modifications as necessary	Not applicable

*A subgroup of ALK+ NSCLC patients (n=25) from the 90mg-180mg QD dosing arm were eligible for inclusion from the total of 71 patients who had previously received crizotinib

** NR for eligible subgroup of patients in phase 2 dosing arms who received brigatinib post-crizotinib. For post-crizotinib patients (n=71) who received phase 1 or 2 doses of brigatinib, median follow-up at time of reporting was 20.0 months.

Table 7.2. Patient Characteristics From the Included Studies[17]

Study	Brigatinib			Ceritinib			Alectinib				Crizotinib		BSC
	ALTA		Study 101	ASCEND-2	ASCEND-5		NP28673	NP28761	ALUR		Hong et al, 2017	PROFILE 1001/1005	Duruisseaux et al, 2017
No. of patients	112	38	25	140	115	116	138	87	72	35	33	120	105
Intervention	Brigatinib 90mg	Brigatinib 180mg	Brigatinib 90mg or 180 mg	Ceritinib	Ceritinib	Chemo	Alectinib	Alectinib	Alectinib	Chemo	Crizotinib	Crizotinib	BSC
Age Median Range 65+	50.5 18-82 NR	56.5 20-81 30 (27.3)	57.0 32-73 5 (20.0)	51.0 29-80 NR	54.0 44-63 26 (22.6)	54.0 47.0-64.0 27 (23.3)	52.0 22-79 NR	54.0 29-79 NR	55.5 21-82 12 (16.7)	59 37-80 10 (28.6)	46.0[g] 21-68 2 (6.1)	50.0 21-78 17 (14.2)	NR NR 36 (34.3)
Gender (%) Male Female	50 (44.6) 62 (55.4)	46 (41.8) 64 (58.2)	14 (56.0) 11 (44.0)	70 (50.0) 70 (50.0)	47 (41.0) 68 (59.0)	55 (47.4) 61 (52.6)	61 (44.2) 77 (55.8)	39 (45.0) 48 (55.0)	41 (56.9) 31 (43.1)	17 (48.6) 18 (51.4)	20 (60.6) 13 (39.4)	65 (54.2) 55 (45.8)	53 (50.5) 52 (49.5)
Race (%) Asian White Other Unknown	39 (34.8) 72 (64.3) 1 (0.9) 0 (0)	30 (27.3) 76 (69.1) 2 (1.8) 2 (1.8)	3 (12.0) 20 (80.0) 2 (8.0)	53 (37.9) 84 (60.0) 3 (2.1) 0 (0)	30 (26.0) 81 (70.0) 2 (2.0) 2 (2.0)	38 (32.8) 68 (58.6) 5 (4.3) 5 (4.3)	36 (26.0) 93 (67.0) 9 (7.0) 0 (0)	7 (8.0) 73 (84.0) 7 (8.0) 0 (0)	5 (6.9) 61 (84.7) 1 (1.5) 5 (6.9)	7 (20.0) 28 (80.0) 0 (0) 0 (0)	33 (100) 0 (0)	39 (32.5) 76 (63.3)	NR

Study	Brigatinib			Ceritinib			Alectinib				Crizotinib		BSC
	ALTA		Study 101	ASCEND-2	ASCEND-5		NP28673	NP28761	ALUR		Hong et al, 2017	PROFILE 1001/ 1005	Duruisseaux et al, 2017
			0 (0)								0 (0) 0 (0)	5 (4.2) 0 (0)	
ECOG PS (%) 0 1 0 or 1 2 3+ Missing	34 (30.4) 71 (63.4) 105 (93.8) 7 (6.3) 0 (0) 0 (0)	45 (40.9) 56 (50.9) 101 (91.8) 9 (8.2) 0 (0) 0 (0)	10 (40.0) 15 (60.0) 25 (100) 0 (0) 0 (0) 0 (0)	42 (30.0) 78 (55.7) 120 (85.7) 20 (14.3) 0 (0) 0 (0)	56 (49.0) 50 (43.0) 106 (92.0) 9 (8.0) 0 (0) 0 (0)	51 (44.0) 60 (51.7) 111 (95.7) 5 (4.3) 0 0	44 (32.0) 81 (59.0) 125 (91.0) 13 (9.0) 0 (0) 0 (0)	30 (35.0) 48 (55.0) 78 (90.0) 9 (10.0) 0 (0) 0 (0)	NR NR 66 (91.7) 6 (8.3) 0 (0) 0 (0)	NR NR 30 (85.7) 5 (14.3) 0 (0) 0 (0)	NR	37 (30.8) 78 (65.0) 103 (95.8) 2 (1.7) 2 (1.7) 1 (0.8)	NR NR 68 (64.7) NR NR 0 (0)
Smoking status (%) Never Former Current Unknown	71 (63.4) 40 (35.7) 0 (0) 1 (0.9)	63 (57.3) 43 (39.1) 4 (3.6) 0 (0)	NR	NR	71 (62.0) 39 (34.0) 4 (3.0) 1 (1.0)	61 (52.6) 51 (44.0) 1 (0.9) 3 (2.6)	96 (70.0) 39 (28.0) 3 (2.0) 0 (0)	54 (62.0) 33 (38.0) 0 (0) 0 (0)	35 (48.6) 35 (48.6) 2 (2.8) 0 (0)	16 (45.7) 17 (48.6) 2 (5.7) 0 (0)	21 (63.6) NR 10 (30.3) 2 (6.1)	83 (69.2) 35 (29.2) 2 (1.7) 0 (0)	59 (56.2) 31 (29.5) 15 (14.3) 0 (0)
Histology (%) Adenocarcinoma Adenosquamous Large-cell carcinoma Squamous cell carcinoma Other	107 (95.5)) 1 (0.9) 1 (0.9) 2 (1.8) 1 (0.9)	108 (98.0) 0 (0) 1 (0.9) 1 (0.9) 0 (0)	24 (96.0) 1 (4.0) 0 (0) 0 (0) 0 (0)	129 (92.1) 1 (0.7) NR 3 (2.1) 7 (5.1)	111 (97.0) NR NR 0 (0) 4 (3.0)	113 (97.4) 0 (0) 0 (0) 2 (1.7) 1 (0.9)	133 (96.0) 2 (1.0) 3 (2.0) 0 (0) 0 (0)	82 (94.3) 2 (2.3) 1 (1.1) 1 (1.1) 1 (1.1)	72 (100) 0 (0) 0 (0) 0 (0) 0 (0)	35 (100) 0 (0) 0 (0) 0 (0) 0 (0)	33 (100) 0 (0) 0 (0) 0 (0) 0 (0)	113 (94.2) NR NR NR 7 (5.8)	93 (88.6) NR NR NR 12 (11.4)
Prior therapy (%) Crizotinib Platinum-based Any chemo	112 (100) NR	110 (100) 80 (72.7)	25 (100) NR	140 (100) 140 (100)	115 (100) 114 (100)	116 (100) 116 (100)	138 (100) NR	87 (100) NR 64 (74.0)	72 (100) 72 (100)	35 (100) 35 (100)	33 (100)	120 (100)	105 (100)

Study	Brigatinib			Ceritinib			Alectinib				Crizotinib		BSC
	ALTA		Study 101	ASCEND-2	ASCEND-5		NP28673	NP28761	ALUR		Hong et al, 2017	PROFILE 1001/ 1005	Duruisseaux et al, 2017
	83 (74.1)	81 (73.6)	17 (68.0)	140 (100)	114 (100)	116 (100)	110 (80.0)		72 (100)	35 (100)	NR NR	115 (95.8) 115 (95.8)	NR NR
Prior radiotherapy to the brain (%)	50 (44.6)	46 (41.8)	7 (28.0)	72 (51.4)	41 (35.7)	42 (36.2)	61 (44.2)	34 (39.1)	23 (31.9)	9 (25.7)	NR	NR	NR
Disease Stage at study entry IIIA IIIB IV Other	 0 (0) 3 (2.7) 109 (97.3) 0 (0)	 1 (0.9) 1 (0.9) 108 (98.2) 0 (0)	 0 (0) 0 (0) 25 (100) 0 (0)	 0 (0) 0 (0) 140 (100) 0 (0)	 0 (0) 1 (1.0) 114 (99.0) (0)	 0 (0) 1 (1.0) 115 (99.0) (0)	 NR 138 (100) were Stage IIIB or IV	 0 (0) 1 (1.0) 86 (99.0) 0 (0)	 NR	 NR	 NR	 NR	 NR
Brain metastases N (%)	80 (71.4)	74 (67.3)	38 (100)	100 (71.4)	65 (57.0)	69 (59.5)	52 (61.0)	52 (60.0)	47 (65.3)	26 (74.3)	15 (45.4)	NR	33 (31.4)

Abbreviations: ALK+, anaplastic lymphoma kinase positive; NSCLC, non-small cell lung cancer; NR, not reported; ECOG PS, Eastern Co-operative Oncology Group Performance Score; BSC, Best Supportive Care

Based on Table 7.2, it is clear that study patient populations were different across many prognostic factors and potential effect modifiers. The median age ranged from 46 years to 59 years, and the proportion of female patients ranged from 39.4% to 59%. Studies included patients who were predominantly White (60.0% to 84.7%) except for the study from Hong and colleagues that was conducted in China and 100% of participants were Asian.[106] While most participants had an ECOG PS of 0 or 1, smoking status was different across studies, with people having never smoked ranging from 45.7% to 70%, and former smokers ranging from 28.0% to 48.6%. Lastly, the proportion of participants with brain metastases varied from 31.4% to 100% across studies, and prior radiotherapy to the brain ranged from 25.7% to 51.4%. The differences in these covariates highlight the need for appropriate adjustment of these variables when conducting comparative analyses.

Indirect Treatment Comparisons: Outcomes

The outcomes of interest for both the MAICs and the NMAs were efficacy, which included OS, PFS, and ORR; and safety and tolerability, which was evaluated by comparing frequency of discontinuation due to adverse events, and frequency of Grade 3 or 4 adverse events.[20] PFS and OS were analyzed using Cox proportional hazards analyses to produce hazard ratios (HRs) with corresponding measures of precision (confidence intervals [CIs] for MAICs and credible intervals [CrIs] for NMAs), whereas ORR, discontinuation due to adverse events, and frequency of Grade 3 or 4 adverse events were analyzed using logistic regression to produce odds ratios (ORs) with corresponding CIs.[20]

Indirect Treatment Comparison Methodology: MAICs

The two available studies evaluating brigatinib in patients with ALK+ NSCLC who previously received crizotinib did not have comparator arms,[1,2] and as a result, naïve comparisons as well as unanchored MAICs were used to compare brigatinib to other pharmacological therapies using individual patient data (IPD) from the brigatinib studies and summary data from studies evaluating other therapies.[20] Two sets of naïve analyses and MAICs were completed: one set using the combined IPD data from Study 101 and the ALTA study, and one set using IPD from only the ALTA study.[20] This is because Study 101 was a dose-finding study with only a proportion of patients included who received therapeutic doses of brigatinib (90mg once daily or 180mg once daily), and Study 101 was missing important covariate information, including smoking status, receipt of prior chemotherapy, and best prior response to crizotinib.[2]

The ITC report authors used MAIC methods from Signorovich and Colleagues and the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Services Document (TSD) 18 to conduct the MAICs.[109,110] A key assumption for the validity of unanchored MAICs is that the analyzed trial populations include all relevant prognostic factors and effect modifiers, and this assumption is very rarely achieved.[109] With regards to the unanchored MAIC, the ITC report authors developed a list of 20 potential covariates for the MAIC that were included in the ALTA study. They then had five clinicians from the United Kingdom with expertise in NSCLC rank the 20 covariates in terms of prognostic impact for survival.[20] They obtained a list of 6 covariates from the ranking process:[20]

- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Presence of brain metastases
- Presence of active brain lesions
- Number of prior anti-cancer regimens
- Best prior response to crizotinib
- Receipt of prior radiotherapy to the brain

The report authors removed presence of active brain lesions and receipt of prior radiotherapy to the brain from the list due to lack of information from comparator studies for presence of active brain lesions and the potential for multicollinearity between the receipt of prior radiotherapy and presence of brain metastases. However, the correlation between these variables was not formally evaluated and proportion of patients with brain metastases and proportion of patients with prior radiotherapy to the brain was different, as seen in Table 7.2.[20] Age, gender, smoking status, receipt of any prior chemotherapy, and whether crizotinib was the last treatment used were added to the list of preferred prognostic factors. The ITC report authors assumed that the efficacy and safety outcomes shared the same prognostic factors, therefore the same covariates were applied to all analyses as allowed by the studies providing comparator summary data. Table 7.3 lists the covariates, the definitions used for each covariate, and the number of studies that evaluated the covariate of interest.

Table 7.3. Covariates Included in the MAIC Analyses[20]

Variable	Definition	Number of Comparator Studies Reporting Factor (n = 8 studies)
ECOG Performance Status	0 or 1 versus 2	7
Brain metastases	Yes versus No	7
Number of prior anti-cancer regimens received	1 or 2 versus ≥ 3	5

Variable	Definition	Number of Comparator Studies Reporting Factor (n = 8 studies)
Best prior response to crizotinib	Partial Response or Complete Response versus Progressive Disease or Stable Disease or Other	2
Age	Continuous	8
Gender	Male versus Female	8
Smoking status	Former or Current versus Never	7
Receipt of any prior chemotherapy	Yes versus No	6
Crizotinib as last treatment before next tyrosine kinase inhibitor	Yes versus No	5

It is important that the studies included in the MAICs have overlapping inclusion and exclusion criteria, and if not, that individuals from the brigatinib studies that would not have been eligible for the comparator studies based on the comparator study inclusion and exclusion criteria, are excluded from the analysis. Table 7.4 lists the study inclusion and exclusion criteria for the brigatinib IPD studies and the comparator studies.

Table 7.4. Brigatinib and Comparator Study Inclusion and Exclusion Criteria[20]

Intervention	Study	Inclusion Criteria	Exclusion Criteria
Brigatinib	ALTA	• Aged ≥18 years; • Locally advanced or metastatic ALK-positive NSCLC; • Investigator-determined disease progression while receiving crizotinib; • ≥1 measurable lesion per RECIST version 1.1; • Adequate organ and hematologic function, and ECOG PS ≤2.	• History or presence of pulmonary interstitial disease or drug-related pneumonitis, or • Symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids
	Study 101	• Aged ≥18 years; • Patients with advanced ALK-rearranged NSCLC • Measurable disease according to RECIST version 1.1; • ECOG PS ≤2; • A minimum life expectancy of 3 months or longer;	• Patients must not have received an investigational agent, systemic anticancer therapy (other than a reversible TKI), or radiotherapy 14 days or fewer before initiating brigatinib; • Reversible TKIs (eg, crizotinib, erlotinib, or gefitinib) were allowed up to 72 h before initiation of brigatinib, if the patient was free of treatment-related toxicity.
Ceritinib	ASCEND-2	• ALK-positive NSCLC who received prior treatment with at least one platinum-based chemotherapy regimen and crizotinib • Locally advanced/metastatic ALK-rearranged NSCLC confirmed by US Food and Drug Administration-approved FISH assay	• Prior treatment with any ALK inhibitor other than crizotinib
	ASCEND-5	• Aged ≥18 years;	• Previous ALK inhibitor therapy other than crizotinib;

Intervention	Study	Inclusion Criteria	Exclusion Criteria
		• ALK-positive NSCLC who had received ≥1 line chemotherapy and previous crizotinib • Locally advanced or metastatic non-small-cell lung cancer; • Confirmed ALK rearrangement; • One or two previous chemotherapy regimens (including a platinum doublet) for advanced disease; • Previous crizotinib therapy; WHO performance status of 0-2, adequate organ function	• Presence of a second malignancy (other than NSCLC that was diagnosed within the past 3 years)
Alectinib	NP28673	• Aged ≥18 years; • Locally advanced stage IIIB or metastatic NSCLC who had experienced progression while receiving crizotinib; • ECOG PS 0-2; Prior treatment with crizotinib and progression (RECIST); • Confirmed ALK rearrangement	• Receipt of any other ALK inhibitors in addition to crizotinib; • Previous malignancy within the past 3 years; history of organ transplant;
	NP28761	• Aged ≥18 years; • ECOG PS 0-2; • Locally advanced or metastatic ALK-positive NSCLC; progressed on crizotinib • US and Canadian patients	• Chemotherapy within 4 weeks or radiotherapy within 2 weeks of study start; • Prior treatment with an ALK inhibitor other than crizotinib; • History of myocardial infarction, congestive heart failure, unstable angina or cardiac arrhythmia
	ALUR	• Advanced or metastatic ALK-positive NSCLC; • ECOG PS 0-2 who have had one prior line each of platinum- based chemo and crizotinib	Not reported
Crizotinib	Hong et al, 2017	• Patients with locally advanced or metastatic ALK-positive NSCLC	Not reported
	PROFILE 1001/1005	• Patients with advanced ALK-positive NSCLC who had been enrolled in PROFILE 1001 or PROFILE 1005 PROFILE 1001: • Advanced malignancies (except leukaemias), histologically proven at diagnosis; • Histologically confirmed advanced malignancies that are sensitive to PF-03241066 inhibition • Solid tumours must have measurable disease • ECOG score of 0 or 1 PROFILE 1005: • Histologically or cytologically proven diagnosis of ALK-positive NSCLC;	PROFILE 1001: • Major surgery, radiation therapy or anti-cancer therapy within 2-4 weeks of starting study treatment • Prior stem cell transplant except of patients with neuroblastoma, lymphoma or myeloma • Active or unstable cardiac disease or heart attack within 3 months of starting study treatment PROFILE 1005: ▪ Received no prior systemic treatment, chemotherapy or EGFR TKI, for advanced NSCLC

Intervention	Study	Inclusion Criteria	Exclusion Criteria
		• May have received pemetrexed or docetaxel from previous Phase 3 trial (A8081007) and discontinued treatment due to RECIST-defined progression	
Best Supportive Care	Duruisseaux et al, 2017	• Aged ≥18 years; • Advanced, metastatic NSCLC; • ALK-positive rearrangement confirmed by FISH; • Not enrolled in current crizotinib trial	• ALK rearrangement not proved by FISH; • No prior crizotinib treatment; • Other tumours than lung cancer; • Other driver oncogenes

ALK = anaplastic lymphoma kinase; CBPD = crizotinib beyond progressive disease; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; NSCLC, non-small cell lung cancer; RECIST, Response evaluation criteria in solid tumours; TKI = tyrosine kinase inhibitor; US = United States; WHO = World Health Organisation.

In general, the inclusion and exclusion criteria were similar between studies; as a result, individuals from the brigatinib studies were not removed from the MAICs.

Indirect Treatment Comparison Methodology: NMAs

Despite having no common comparator arm between the included brigatinib studies and the comparator studies, NMAs were completed using the results of the MAICs to create "virtual studies" that acted as head-to-head comparisons to create connected networks in the NMAs.[20] Conventional Bayesian methods were used to conduct the analyses using both fixed effect and random effects models, and Deviance Information Criterion (DIC) values were used to identify the better fitting model for each endpoint.[20]

Results were presented as forest plots for each outcome with estimates of treatment effect for all pairwise comparisons between brigatinib and comparators in the network, as HRs and ORs with corresponding 95% credible intervals (CrI).[20]

Indirect Treatment Comparison Results: MAICs

The efficacy and safety results, summarized by outcome and brigatinib data (combined ALTA and Study 101 IPD; ALTA IPD only), can be found in Table 7.10.

Efficacy

PFS

Table 7.5 lists the study level median PFS. Brigatinib was associated with a longer PFS compared to the comparator agents. With regards to the MAIC analyses, PFS was statistically significantly improved in patients who received brigatinib (investigator-assessed [INV] and independent review committee-assessed [IRC]) compared to ceritinib, alectinib, and chemotherapy, but was not statistically different from crizotinib retreatment (Table 7.10).[20] Unanchored MAIC results were generally consistent between the pooled brigatinib study data and the ALTA study only; comparisons using ALTA study data were associated with wider CIs.

Table 7.5. Study Level Median PFS[97]

Study	Treatment	Measure	Median Months	95% Confidence Interval
ALTA	Brigatinib 180mg	INV	15.6	11.1 - 22.3
		IRC	16.7	12.6 - 22.8
ALTA		INV	9.2	7.4 - 11.1

Study	Treatment	Measure	Median Months	95% Confidence Interval
	Brigatinib 90mg	IRC	9.2	7.4 - 12.8
Study 101	Brigatinib 90 - 180mg	INV	11.9	3.5 - 21.2
Study 101	Brigatinib 90mg	INV	16.3	9.2 - NE
ASCEND-2	Ceritinib	INV	5.7	5.4 - 7.6
ASCEND-2		IRC	7.2	5.4 - 9.0
ASCEND-5		INV	6.7	4.4 - 7.9
ASCEND-5		IRC	5.4	4.1 - 6.9
ALUR	Alectinib	INV	9.6	6.9 - 12.2
ALUR		IRC	7.1	6.3 - 10.8
NP28673		IRC	8.9	5.6 - 12.8
NP28761		IRC	8.2	6.3 - 12.6
ASCEND-5	Chemotherapy	INV	1.6	1.4 - 2.6
ASCEND-5		IRC	1.6	1.4 - 2.8
ALUR		INV	1.4	1.3 - 1.6
ALUR		IRC	1.6	1.3 - 4.1
Hong (2017)[106]	Crizotinib Retreatment	IRC	16 weeks	11.9 - 20.1 weeks

INV = investigator-assessed; IRC = independent review committee-assessed; NE = not estimable

OS

Study level median OS is reported in Table 7.6. OS was statistically significantly improved in patients who received brigatinib compared to those who received ceritinib, crizotinib retreatment, and best supportive care in the MAIC analyses. Results comparing brigatinib to alectinib and to chemotherapy with regards to OS were inconsistent; when compared with alectinib in the ALUR and NP28761, brigatinib statistically improved OS compared to alectinib, but no statistical difference was found between brigatinib and alectinib with the NP28673 study. For chemotherapy, brigatinib was associated with a statistical improvement in OS when compared to chemotherapy from the ASCEND-5 study, but no statistical difference was found with the ALUR comparator study. Similarly to the PFS estimates, results were generally consistent between the ALTA study data and the pooled brigatinib study data; comparisons using ALTA study data were associated with wider CIs.

Table 7.6. Study Level Median OS[97]

Study	Treatment	Median Months	95% Confidence Interval
ALTA	Brigatinib 180mg	27.6	27.6 - NE
ALTA	Brigatinib 90mg	Not reached	20.2 - NE
Study 101	Brigatinib 180mg	Not reached	Range: 1.4 - 24.3
Study 101	Brigatinib 90mg	34.4	9.9 - 47.6
ASCEND-2	Ceritinib	14.9	13.5 - NE
ASCEND-5		18.1	13.4 - 23.9
ALUR[39]	Alectinib	12.6	9.7 - NE
NP28673		26.0	21.5 - NE
NP28761		22.7	17.2 - NE
ASCEND-5	Chemotherapy	20.1	11.9 - 25.1
Duruisseaux 2017[107]	Best Supportive Care	1.5	0.8 - 2.1

NE = not estimable

ORR

Only the ALTA study provided information for brigatinib and ORR because ORR was not evaluated in Study 101. As listed in Table 7.7, a larger proportion of patients who received brigatinib achieved an ORR of partial response or complete response. Individuals who received brigatinib were statistically significantly more likely to achieve an ORR compared with ceritinib and with chemotherapy. When compared with alectinib, two of the three analyses demonstrated no statistical difference between alectinib and brigatinib.

Table 7.7. Study Level ORRs[20]

Study	Treatment	Measure	n	N	%
ALTA	Brigatinib	INV	62	110	56.4
		IRC	62	110	56.4
ASCEND-2	Ceritinib	INV	54	140	38.6
ASCEND-5		IRC	45	115	39.1
ALUR	Alectinib	INV	27	72	37.5
NP28673		IRC	62	138	44.9
NP28761		IRC	35	87	40.2
ASCEND-5	Chemotherapy	IRC	8	116	6.9
ALUR		INV	1	35	2.9

Safety

Discontinuation Due to Adverse Events

Discontinuation due to adverse events was not evaluated in Study 101, so only the ALTA study provided information on this comparison. Table 7.8 lists the proportion of patients who discontinued therapy due to adverse events. Among agents with more than one study, results were inconsistent. For example, 15.7% of patients on ceritinib discontinued therapy due to adverse events in the ASCEND-5 trial, whereas 7.9% discontinued ceritinib in the ASCEND-2 trial. Discontinuation ranged from 2.3% to 8.0% for alectinib. No statistically significant differences were found between brigatinib and comparator therapies for discontinuation due to adverse events in the MAIC analyses, except for when compared with alectinib in the NP28761 study, where individuals receiving brigatinib were statistically significantly less likely to discontinue brigatinib due to adverse events (Table 7.10).

Table 7.8. Study Level Discontinuations Due to Adverse Events[20]

Study	Treatment	n	N	%
ALTA	Brigatinib	10	110	9.1
ASCEND-2	Ceritinib	11*	140	7.9
ASCEND-5		18	115	15.7
ALUR	Alectinib	4	70	5.7
NP28673		11	138	8.0
NP28761		2	87	2.3
ASCEND-5	Chemotherapy	8	113	7.1
ALUR		3	34	7

*Back-calculated from %

Frequency of Grade 3 or 4 Adverse Events

Similarly to ORR and discontinuation due to adverse events, frequency of Grade 3 or 4 adverse events was not evaluated in Study 101, so only the ALTA study provided information on this comparison. The proportion of patients who experienced Grade 3 or 4 adverse events is listed in Table 7.9. The proportion who experienced adverse events varied between studies, even among those evaluating the same agent. Results from the MAIC analysis indicate that people on brigatinib were statistically significantly more likely to experience Grade 3 or 4 adverse events compared to alectinib. Comparisons with chemotherapy were inconsistent, with one comparison finding people on brigatinib were statistically significantly less likely to experience Grade 3 or 4 adverse events (ALUR Study), and another comparison finding that people on brigatinib were statistically significantly more likely to experience Grade 3 or 4 adverse events

compared with chemotherapy (ASCEND-5 Study). No differences were found between brigatinib and ceritinib (Table 7.10).

Table 7.9. Study Level Frequency of Grade 3 or 4 Adverse Events[20]

Study	Treatment	n	N	%	Notes
ALTA	Brigatinib	75	110	68.2	
ASCEND-2	Ceritinib	100	140	71.4	Any Grade 3+
ASCEND-5		89	115	77.4	Grade 3 and 4
ALUR	Alectinib	19	70	27.1	Grade 3 - 5
NP28761		36*	87	41.3	
ASCEND-5	Chemotherapy	91	113	80.5	Grade 3 and 4
ALUR		14	34	41.2	Grade 3 - 5

*Back-calculated from %

Table 7.10. Summary of MAIC for Efficacy and Safety Outcomes[20]

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
Ceritinib	ASCEND-2	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes)	PFS INV HR: 2.59 [1.87 - 3.59] OS HR: 2.15 [1.39 - 3.31] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS INV HR: 2.62 [1.77 - 3.88] OS HR: 2.31 [1.37 - 3.89] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	67.1
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes) Number of prior regimens (1-2 vs ≥3)	PFS INV HR: 2.61 [1.84 - 3.70] OS HR: 2.12 [1.34 - 3.35] ORR INV OR: 0.49 [0.29 - 0.81] Discontinuation OR: 0.85 [0.35 - 2.12] Grade 3 or 4 AEs OR: 1.17 [0.68 - 2.01]	PFS INV HR: 2.77 [1.81 - 4.23] OS HR: 2.44 [1.39 - 4.29] ORR INV OR: 0.54 [0.30 - 0.97] Discontinuation OR: 0.69 [0.26 - 1.91] Grade 3 or 4 AEs OR: 1.05 [0.55 - 1.97]	110	58.9

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
	ASCEND-5	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes)	PFS: Not Reported OS HR: 2.06 [1.35 - 3.16] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 2.00 [1.23 - 3.23] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	76.5
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes) Number of prior regimens (1-2 vs ≥3) Smoking status (Former/current vs Never)	PFS IRC HR: 3.52 [2.43 - 5.10] OS HR: 2.07 [1.32 - 3.26] ORR IRC OR: 0.50 [0.29 - 0.84] Discontinuation OR: 1.86 [0.83 - 4.37] Grade 3 or 4 AEs OR: 1.60 [0.89 - 2.91]	PFS IRC HR: 5.19 [2.79 - 9.65] OS HR: 2.64 [1.34 - 5.22] ORR IRC OR: 0.38 [0.18 - 0.80] Discontinuation OR: 3.05 [0.85 - 18.12] Grade 3 or 4 AEs OR: 2.14 [0.96 - 4.69]	110	30.4
Alectinib	ALUR	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes)	PFS INV HR: 1.85 [1.13 - 3.05] OS HR: 2.20 [1.16 - 4.18] ORR: Not Reported Discontinuation OR: Not Reported	PFS INV HR: 1.87 [1.09 - 3.22] OS HR: 2.20 [1.09 - 4.44] ORR: Not Reported Discontinuation OR: Not Reported	135	89.5

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
				Grade 3 or 4 AEs OR: Not Reported	Grade 3 or 4 AEs OR: Not Reported		
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Smoking status (Former/current vs Never)	PFS INV HR: 1.86 [1.10 - 3.13] OS HR: 2.24 [1.15 - 4.35] ORR INV OR: 0.46 [0.25 - 0.84] Discontinuation OR: 0.61 [0.16 - 1.90] Grade 3 or 4 AEs OR: 0.17 [0.09 - 0.33]	PFS INV HR: 2.10 [1.18 - 3.74] OS HR: 2.81 [1.29 - 6.11] ORR INV OR: 0.53 [0.27 - 1.02] Discontinuation OR: 0.37 [0.10 - 1.16] Grade 3 or 4 AEs OR: 0.13 [0.06 - 0.27]	110	72.6
	NP28673	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes)	PFS INV HR: 1.42 [1.05 - 1.92] OS HR: 1.41 [0.97 - 2.06] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS INV HR: 1.39 [1.02 - 1.89] OS HR: 1.40 [0.96 - 2.06] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	115.8
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Number of prior regimens (1-2 vs ≥3) Smoking status (Former/current vs Never) Best prior response to crizotinib (PR/CR vs other)	PFS INV HR: 1.47 [1.06 - 2.06] OS HR: 1.44 [0.95 - 2.18] ORR IRC OR: 0.57 [0.34 - 0.95]	PFS INV HR: 1.62 [1.12 - 2.34] OS HR: 1.44 [0.92 - 2.24] ORR IRC OR: 0.58 [0.33 - 1.01]	100	65.2

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
				Discontinuation OR: 0.88 [0.35 - 2.26] Grade 3 or 4 AEs OR: Not Reported	Discontinuation OR: 0.87 [0.33 - 2.40] Grade 3 or 4 AEs OR: Not Reported		
	NP28761	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes)	PFS: Not Reported OS HR: 1.68 [1.08 - 2.61] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 1.58 [1.02 - 2.46] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	125.6
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Smoking status (Former/current vs Never)	PFS IRC HR: 1.70 [1.16 - 2.49] OS HR: 1.69 [1.06 - 2.69] ORR IRC OR: 0.52 [0.29 - 0.92] Discontinuation OR: 0.24 [0.04 - 0.92] Grade 3 or 4 AEs OR: 0.33 [0.18 - 0.59]	PFS IRC HR: 1.70 [1.16 - 2.51] OS HR: 1.63 [1.02 - 2.60] ORR IRC OR: 0.51 [0.28 - 0.90] Discontinuation OR: 0.23 [0.04 - 0.92] Grade 3 or 4 AEs OR: 0.13 [0.18 - 0.59]	110	101.5
Crizotinib Retreatment	Hong (2017)	ALTA	Age (Continuous) Gender (Female vs Male) Brain metastases (No vs Yes) Crizotinib as last treatment (No vs Yes) Smoking status (Former/current vs Never) Number of prior regimens (1-2 vs ≥3)	PFS IRC HR: 0.82 [0.49 - 1.35] OS: Not Reported	PFS IRC HR: 0.89 [0.50 - 1.58] OS: Not Reported	110	38.4

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
				ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported		
	Ou (2014)	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes)	PFS: Not Reported OS HR: 2.57 [1.80 - 3.67] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 3.61 [2.30 - 5.66] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	70.2
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes) Smoking status (Former/current vs Never) Best prior response to crizotinib (PR/CR vs other)	PFS: Not Reported OS HR: 2.63 [2.77 - 3.93] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 4.17 [2.44 - 7.12] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	100	53.4
Chemotherapy	ASCEND-5	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes)	PFS: Not Reported OS HR: 2.22 [1.46 - 3.37] ORR: Not Reported	PFS: Not Reported OS HR: 2.30 [1.41 - 3.73] ORR: Not Reported	135	78.8

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
				Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported		
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Crizotinib as last treatment (No vs Yes) Number of prior regimens (1-2 vs ≥3) Smoking status (Former/current vs Never)	PFS IRC HR: 6.68 [4.52 - 9.88] OS HR: 2.25 [1.44 - 3.51] ORR IRC OR: 0.06 [0.02 - 0.12] Discontinuation OR: 0.76 [0.28 - 2.01] Grade 3 or 4 AEs OR: 1.93 [1.05 - 3.61]	PFS IRC HR: 8.90 [4.47 - 17.73] OS HR: 2.73 [1.39 - 5.36] ORR IRC OR: 0.05 [0.02 - 0.12] Discontinuation OR: 1.09 [0.28 - 6.07] Grade 3 or 4 AEs OR: 2.57 [1.14 - 5.74]	110	31.6
	ALUR	Pooled ALTA/Study 101	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes)	PFS INV HR: 9.36 [5.63 - 15.57] OS HR: 1.88 [0.81 - 4.38] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS INV HR: 8.21 [4.73 - 14.25] OS HR: 1.96 [0.79 - 4.84] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	70.9
		ALTA	Age (Continuous) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Prior chemotherapy (No vs Yes) Smoking status (Former/current vs Never)	PFS INV HR: 9.16 [5.37 - 15.62] OS HR: 1.88 [0.79 - 4.46]	PFS INV HR: 7.89 [4.40 - 14.15] OS HR: 2.29 [0.87 - 6.01]	110	56.7

Comparator	Comparator Study	Brigatinib Data	Covariates Included in the Model	Naïve HR/OR [95% CI]	MAIC-HR/OR [95% CI]	Brigatinib Sample Size	ESS from MAIC
				ORR INV OR: 0.02 [<0.01 - 0.11] Discontinuation OR: 0.97 [0.21 - 3.40] Grade 3 or 4 AEs OR: 0.33 [0.15 - 0.72]	ORR INV OR: 0.03 [<0.01 - 0.15] Discontinuation OR: 0.70 [0.15 - 2.61] Grade 3 or 4 AEs OR: 0.27 [0.11 - 0.63]		
Best Supportive Care	Duruisseaux (2017)	Pooled ALTA/Study 101	Age (<65 vs ≥65) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Crizotinib as last treatment (No vs Yes)	PFS: Not Reported OS HR: 6.54 [4.55 - 9.38] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 5.09 [3.28 - 7.88] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	135	33.7
		ALTA	Age (<65 vs ≥65) Gender (Female vs Male) ECOG PS (0-1 vs 2+) Brain metastases (No vs Yes) Crizotinib as last treatment (No vs Yes) Smoking status (Former/current vs Never) Best prior response to crizotinib (PR/CR vs other)	PFS: Not Reported OS HR: 6.53 [4.42 - 9.63] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	PFS: Not Reported OS HR: 5.71 [3.43 - 9.53] ORR: Not Reported Discontinuation OR: Not Reported Grade 3 or 4 AEs OR: Not Reported	110	30.0

AEs = adverse events; CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; HR = hazard ratio; INV = investigator-assessed; IRC = Independent Review Committee-assessed; MAIC = matching-adjusted indirect comparison; OR = odds ratio; ORR = objective response rate; OS = overall survival; other = stable disease and progressive disease; PFS = progression-free survival; PR = partial response.

Indirect Treatment Comparison Results: NMAs

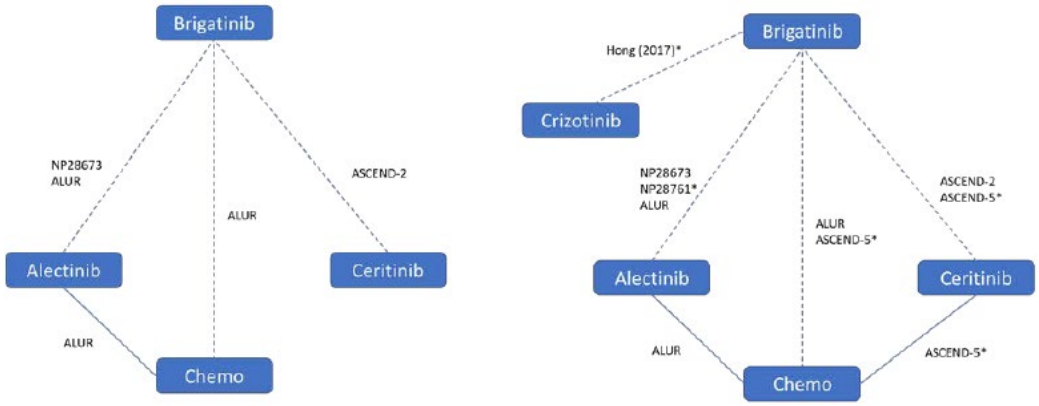
The efficacy and safety results, summarized by outcome and brigatinib data (combined ALTA and Study 101 IPD; ALTA IPD only), can be found in Table 7.11.

Efficacy

PFS

The study networks for PFS are provided in Figure 7.1. Brigatinib was associated with statistically significantly longer PFS compared with alectinib, ceritinib, crizotinib retreatment, and chemotherapy. These results were consistent across the brigatinib pooled data and ALTA data only, and with both fixed effect and random effects models.

Figure 7.1. Networks of Evidence for PFS (Left: Pooled Brigatinib Data; Right: ALTA Study)[20]

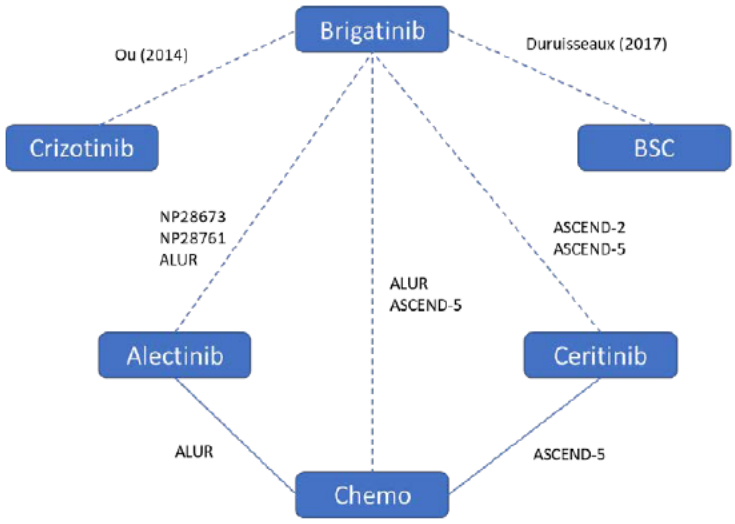


Key: dashed lines represent MAIC-HRs; solid lines represent reported head-to-head HRs.

OS

Figure 7.2 provides the network of evidence for OS. Similarly to PFS, brigatinib was associated with statistically significantly longer OS compared with alectinib, ceritinib, crizotinib retreatment, chemotherapy, and best supportive care. These results were also consistent across the brigatinib pooled data and ALTA data only, and with both fixed effect and random effects models.

Figure 7.2. Network of Evidence for OS (Both the Pooled Brigatinib Data and the ALTA Study)[20]

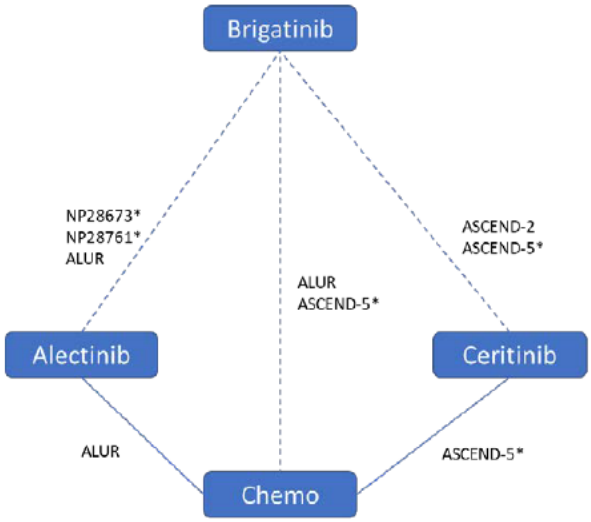


Key: dashed lines represent MAIC-HRs; solid lines represent reported head-to-head HRs.

ORR

Figure 7.3 provides the network of evidence for comparison of ORR. NMAs were performed with the brigatinib ALTA study data only because ORR was not evaluated in Study 101. Only studies evaluating ceritinib, alectinib, and chemotherapy had ORR data and were able to be compared to brigatinib. Individuals on brigatinib were statistically significantly more likely to achieve an ORR compared to alectinib, ceritinib, and chemotherapy. The results were consistent across fixed effect and random effects models.

Figure 7.3. Network of Evidence for ORR (ALTA Study)[20]



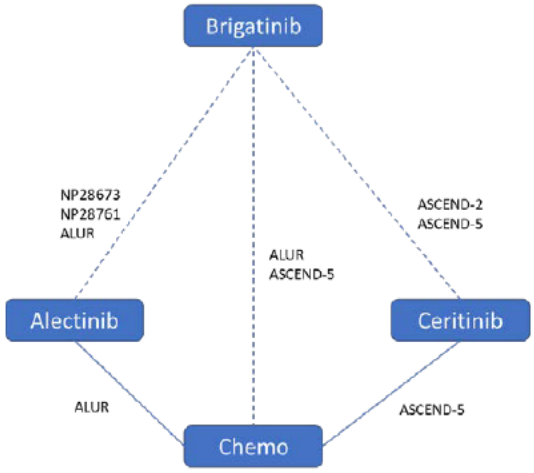
Key: * denotes IRC-assessed ORR (INV-assessed ORR otherwise); dashed lines represent MAIC-ORs; solid lines represent reported head-to-head ORs.

Safety

Discontinuation Due to Adverse Events and Frequency of Grade 3 or 4 Adverse Events

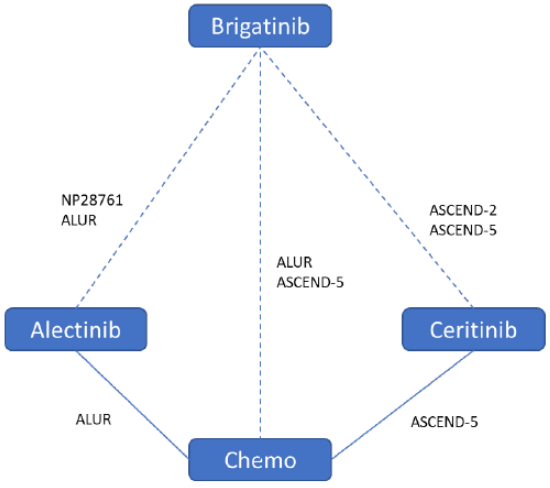
Discontinuation of brigatinib due to adverse events and frequency of Grade 3 or 4 adverse events were only reported in the ALTA study, therefore comparisons could not be made with the brigatinib pooled data. In addition, information on discontinuations and Grade 3 or 4 adverse events were not available for crizotinib retreatment or best supportive care. No statistically significant difference was found between brigatinib and alectinib, ceritinib, or chemotherapy for discontinuation due to adverse events or for occurrence of Grade 3 or 4 adverse events in the random effects models. People receiving brigatinib were statistically significantly more likely to discontinue therapy due to adverse events and experience Grade 3 or 4 adverse events compared to alectinib in the fixed effect models. Figures 7.4 and 7.5 provide the evidence networks for discontinuation of adverse events and frequency of Grade 3 or 4 adverse events, respectively.

Figure 7.4. Network of Evidence for Discontinuation Due to Adverse Events (ALTA Study)[20]



Key: dashed lines represent MAIC-ORs; solid lines represent reported head-to-head ORs.

Figure 7.5. Network of Evidence for Frequency of Grade 3 or 4 Adverse Events (ALTA Study)[20]



Key: dashed lines represent MAIC-ORs; solid lines represent reported head-to-head ORs.

Table 7.11. Efficacy and Safety Results with NMAs[20]

Comparator	Brigatinib Data	PFS HR [95% CrI]	OS HR [95% CrI]	ORR OR [95% CrI]	Discontinuation Due to AE OR [95% CrI]	Grade 3 or 4 AE OR [95% CrI]
Ceritinib	Pooled ALTA/Study 101	FE: 0.38 [0.26 – 0.57] RE: 0.38 [0.20 – 0.70]	FE: 0.47 [0.35 – 0.64] RE: 0.47 [0.33 – 0.69]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
	ALTA	FE: 0.27 [0.20 – 0.36] RE: 0.27 [0.18 – 0.38]	FE: 0.41 [0.29 – 0.59] RE: 0.41 [0.26 – 0.65]	FE: 2.20 [1.43 – 3.36] RE: 2.26 [1.34 – 3.98]	FE: 0.75 [0.38 – 1.47] RE: 0.72 [0.25 – 1.94]	FE: 1.07 [0.69 – 1.63] RE: 0.87 [0.22 – 3.41]
Alectinib	Pooled ALTA/Study 101	FE: 0.68 [0.52 – 0.88] RE: 0.67 [0.44 – 1.00]	FE: 0.62 [0.48 – 0.80] RE: 0.61 [0.43 – 0.84]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
	ALTA	FE: 0.60 [0.48 – 0.76] RE: 0.60 [0.45 – 0.82]	FE: 0.57 [0.43 – 0.77] RE: 0.56 [0.36 – 0.81]	FE: 1.82 [1.30 – 2.57] RE: 1.81 [1.15 – 2.87]	FE: 2.00 [1.06 – 3.81] RE: 2.08 [0.86 – 5.33]	FE: 3.64 [2.41 – 5.52] RE: 3.72 [0.94 – 15.11]
Crizotinib retreatment	Pooled ALTA/Study 101	FE: Not Reported RE: Not Reported	FE: 0.28 [0.18 – 0.43] RE: 0.28 [0.15 – 0.50]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
	ALTA	FE: 0.26 [0.16 – 0.45] RE: 0.26 [0.14 – 0.51]	FE: 0.24 [0.14 – 0.41] RE: 0.24 [0.12 – 0.49]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
Chemotherapy	Pooled ALTA/Study 101	FE: 0.11 [0.07 – 0.17] RE: 0.11 [0.06 – 0.20]	FE: 0.48 [0.35 – 0.65] RE: 0.48 [0.33 – 0.72]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
	ALTA	FE: 0.12 [0.09 – 0.16] RE: 0.12 [0.08 – 0.17]	FE: 0.42 [0.29 – 0.61] RE: 0.42 [0.27 – 0.68]	FE: 21.98 [11.97 – 39.92] RE: 22.63 [11.36 – 47.17]	FE: 1.46 [0.72 – 2.89] RE: 1.42 [0.51 – 3.63]	FE: 1.07 [0.69 – 1.63] RE: 1.17 [0.34 – 4.21]
Best Supportive Care	Pooled ALTA/Study 101	FE: Not Reported RE: Not Reported	FE: 0.20 [0.13 – 0.30] RE: 0.20 [0.11 – 0.35]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported
	ALTA	FE: Not Reported RE: Not Reported	FE: 0.18 [0.11 – 0.29] RE: 0.17 [0.09 – 0.36]	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported	FE: Not Reported RE: Not Reported

AE = adverse event; CrI = credible interval; FE: fixed effect model; HR = hazard ratio; OR = odds ratio; RE: random effects model

7.1.3 Critical Appraisal of the Indirect Treatment Comparison

The quality of the manufacturer-submitted ITC was assessed based on the 2014 ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire[21] to Assess Relevance and Credibility. A summary of the quality assessment is provided in Table 7.12.

The submitted ITC used naïve comparisons, unanchored MAICs, and NMA using data from the unanchored MAICs to compare brigatinib to alectinib, ceritinib, chemotherapy, crizotinib retreatment, and best supportive care with regards to efficacy and safety outcomes.[20] There are a number of concerns regarding these analyses that must be considered:

- Unanchored MAICs are rarely able to overcome the strict assumption that all relevant prognostic factors and effect modifiers have been captured in the included studies. The bias resulting from missing covariates is very difficult to quantify, and as a result, it is unclear what impact the missing covariates have on the results of the MAICs. Some examples of covariates not included in the analysis that may have impacted the results include receipt of prior radiotherapy to the brain, duration of illness, and presence of active brain lesions. In addition, important covariates were not captured in all of the included studies, making some individual MAICs more susceptible to additional bias.
- The assumption that the efficacy and safety outcomes share the same prognostic factors is also a limitation. Some examples of covariates that may have impacted the safety outcome analyses include previous discontinuation of therapy due to adverse events or previous reduction in dosage due to adverse events.
- Another indication of the appropriateness of MAICs is the effective sample size for the analysis, which serves as an indication of the similarity between the two studies within the MAIC. In particular, the effective sample size was reduced considerably from the original sample size when the brigatinib data was compared with the observational studies by Hong et al, Ou et al, and Duruisseau et al, as well as some comparisons between the brigatinib data and the ASCEND-5 study, as is seen in Table 7.10.
- The NMA is inherently flawed given the use of unanchored MAIC data to create "virtual studies" to represent head-to-head trials within the networks. As mentioned in the ISPOR document, "If some interventions of interest are not part of the same network, then it is not possible to perform an indirect comparison of treatment effects of these interventions without a substantial risk of bias…"[21] because it is not possible to compare relative treatment effects without a common comparator. In addition, a number of the NMA comparisons resulted in patients on brigatinib being counted more than once in the analysis, falsely improving precision in the estimates associated with brigatinib.
- While health-related quality of life outcomes were evaluated in some of the studies included in the ITC, they were not reported on in the ITC report.
- The submitted SLR and ITC were completed by external consultancy groups hired by the manufacturer. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review.

Table 7.12: Adapted ISPOR Questionnaire to assess the relevance and credibility of an ITC or NMA.[21]

IPSOR Questions	Details and Comments
1. Is the population relevant?	Yes. The patients in the included studies align with the target population of interest: patients with ALK+ NSCLC who have progressed on crizotinib.
2. Are any critical interventions missing?	No. The ITC included all relevant treatment comparators at appropriate doses, schedules, and modes of administration.
3. Are any critical outcomes missing?	Yes. Although relevant efficacy and safety outcomes were considered, HRQoL was not included in the analysis even though it was evaluated in some of the included studies. Rationale for why it was not evaluated in the ITC was not provided.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes. Many of the studies had study sites in Canada.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes, in part. The systematic review appeared comprehensive in terms of the approach used to search for evidence. It was unclear why the ITC report authors excluded one of the identified observational studies from the SLR, however (Kayaniyil et al, 2016).
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	No. The authors used unanchored MAIC to examine the study objectives. They then used the results of the unanchored MAICs to create "virtual" head-to-head studies to conduct NMAs
7. Is it apparent that poor quality studies were included leading to bias?	Unclear. The important sources of bias for the included clinical studies were performance bias and detection bias. Critical appraisal of the included observational studies was not provided, therefore it is unclear what the quality of these studies was, and whether it would have impacted the results of the analyses.
8. Is it likely that bias was introduced by selective reporting of outcomes in the studies?	Unlikely. Only the ALUR study was unpublished at the time the SLR and ITCs were completed, therefore it was not possible to evaluate selective reporting of outcomes for this study. All other studies appeared to report their planned outcomes.
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?	Yes. A number of patient characteristics were imbalanced between studies including brain metastases, prior radiotherapy to the brain, and smoking status. A number of covariates were missing from studies resulting in an inability to account for these covariates in the MAICs. Other potentially important covariates that were not considered were duration of illness and presence of active brain lesions. Prognostic factors and effect modifiers were considered the same for both the efficacy and safety analyses. Missing covariates for the safety outcomes such as previous discontinuation of therapy due to adverse events or previous reduction in dosage due to adverse events were not included in the analysis.
10. If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Not reported.
11. Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	No. Naïve comparisons, unanchored MAICs, and NMAs based on the unanchored MAICs were performed.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in	Not applicable (analysis was an unanchored MAIC and an NMA using data from the unanchored MAICs).

IPSOR Questions	Details and Comments
treatment effects (i.e. consistency) evaluated or discussed?	
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable (analysis was an unanchored MAIC and an NMA using data from the unanchored MAICs).
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 in the analysis?	The authors used unanchored MAIC analyses to attempt to control for differences in effect modifiers and prognostic factors between the Brigatinib studies with IPD, and the studies providing comparator summary data. Availability of covariates varied between the studies providing comparator summary data, and important covariates were missing from the efficacy and safety analyses. The authors then used the results of the unanchored MAICs to conduct NMAs, therefore the flaws of the MAICs would be retained in the NMAs.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	No. Only Deviance Information Criterion (DIC) values were used to determine the better fitting model between fixed effect and random effects models.
16. If random effects model was used, were assumptions about heterogeneity explored or discussed?	No.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes.
20. Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Not applicable (analysis was an unanchored MAIC and an NMA using data from the unanchored MAICs).
21. Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Yes.
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?	No.
24. Are the conclusions fair and balanced?	No. The conclusions cannot be considered fair and balanced due to differences in patient characteristics between the studies, the limitations associated with unanchored MAICs, and the use of the unanchored MAICs to conduct NMAs.
25. Were there any potential conflicts of interest?	Not reported.

IPSOR Questions	Details and Comments
26. If yes, were steps taken to address these?	Not applicable.

7.1.4 Summary

A manufacturer-submitted ITC which compared brigatinib to alectinib, ceritinib, chemotherapy, crizotinib retreatment, and best supportive care for patients with ALK+ NSCLC who progressed on crizotinib was summarized and critically appraised using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[20,21] The unanchored MAICs found that brigatinib statistically significantly improved PFS compared to ceritinib, alectinib, and chemotherapy, but no difference was found with crizotinib retreatment. Brigatinib also statistically significantly improved OS compared with ceritinib and crizotinib retreatment, but results were inconsistent when compared with alectinib and chemotherapy. No difference was found when brigatinib was compared to ceritinib or chemotherapy for discontinuation due to adverse events, and inconsistent results were seen when compared with alectinib. Brigatinib was associated with a lower likelihood of Grade 3 or 4 adverse events compared to alectinib; no difference was found when comparing brigatinib to ceritinib, and inconsistent results were seen when compared to chemotherapy. Health-related quality of life data were not reported. Concerns were noted related to the internal validity of the results. The main limitations of the ITC included the use of unanchored MAICs, given the likelihood of bias due to missing prognostic factors and effect modifiers. The use of unanchored MAICs as head-to-head studies in the NMAs is a serious limitation of the NMAs, along with the double-counting of patients on brigatinib resulting in falsely improved precision in the NMAs. Because if these limitations, the unanchored MAIC estimates are most appropriate for the economic analysis, however, the comparative efficacy and safety estimates obtained are likely biased due to these limitations, 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.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. **Literature search via OVID platform**

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2018, Embase 1974 to 2018 December 14, Ovid MEDLINE(R) ALL 1946 to December 14, 2018

#	Searches	Results
1	(brigatinib* or Alunbrig* or AP26113 or AP-26113 or HYW8DB273J).ti,ab,ot,kf,kw,hw,nm.	669
2	1 use medall	96
3	1 use cctr	35
4	*Brigatinib/ or (brigatinib* or Alunbrig* or AP26113 or AP-26113 or HYW8DB273J).ti,ab,kw,dq.	435
5	4 use oemezd	310
6	5 and (conference review or conference abstract).pt.	121
7	limit 6 to english language	121
8	limit 7 to yr="2013 -Current"	112
9	5 not (conference review or conference abstract).pt.	189
10	2 or 3 or 9	320
11	limit 10 to english language	310
12	remove duplicates from 11	218
13	8 or 12	330

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search **#1 AND #2** Filters: **English**	5
#3	Search **#1 AND #2**	5
#2	Search **publisher[sb]**	538820
#1	Search **brigatinib*[tiab] OR Alunbrig*[tiab] OR AP26113[tiab] OR AP-26113[tiab] OR HYW8DB273J[tiab] OR HYW8DB273J[rn]**	96

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

4. Grey Literature search via:

Clinical Trial Registries:

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

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

Search: Alunbrig/brigatinib, non-small cell lung cancer

Select international agencies including:

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

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

Search: Alunbrig/brigatinib, non-small cell lung cancer

Conference abstracts:

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

American Society of Hematology (ASH)
http://www.bloodjournal.org/page/ash-annual-meeting-abstracts

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

Search: Alunbrig/brigatinib, non-small cell lung cancer – last 5 years

Detailed Methodology

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Alunbrig/brigatinib.

No methodological filters were applied to limit retrieval to any particular publication type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of May 2, 2019.

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

Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

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