pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Brigatinib (Alunbrig)

Submitted Reimbursement Request:
As a monotherapy for the treatment of adult patients with anaplastic lymphoma kinase positive locally advanced or metastatic non-small cell lung cancer who have progressed on or who were intolerant to an ALK inhibitor (crizotinib)

Submitted by:
Takeda Canada Inc.

Manufactured by:
Takeda Canada Inc.

NOC/c Date:
July 26, 2018

Submission Date:
October 24, 2018

Initial Recommendation Issued:
May 31, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Brigatinib (oral) costs $336.96 per 90 mg or per 180 mg. 90 mg once daily for the first 7 days; then 180 mg once daily. Cost per 28-day cycle: $9,435.00.

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions***

☒ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC does not recommend reimbursement of brigatinib (Alunbrig) for the treatment of 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 an ALK inhibitor (crizotinib).

pERC made this recommendation because it was not satisfied that there is a net clinical benefit of brigatinib compared with alectinib, ceritinib, or single-agent chemotherapy given the limitations in the evidence from the available phase II clinical trial. While pERC was confident that brigatinib produces a tumour response, pERC was unable to determine how brigatinib compares with other available treatments given the lack of robust comparative data on outcomes important to decision-making such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL). Given the availability of other treatments following progression on or intolerance to crizotinib, pERC was uncertain whether brigatinib addresses an unmet need.

pERC noted that brigatinib aligned with patient values in that it produced anti-tumour activity, with manageable side effects, and offers an additional treatment choice. However, the Committee was unable to make conclusions on the benefit of brigatinib compared with other options.

pERC could not draw a conclusion on the cost-effectiveness of brigatinib

	compared with alectinib, ceritinib, or single-agent chemotherapy due to the uncertainty surrounding the incremental survival benefits used in the economic model.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC considered that it is possible to conduct a phase III randomized controlled trial (RCT) in the requested reimbursement patient population. pERC noted that new clinical data comparing brigatinib with currently available treatments in Canada for patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS, and QoL, are available.

SUMMARY OF pERC DELIBERATIONS

In 2018, it was estimated that there were 28,600 new cases of lung cancer diagnosed, and 21,100 deaths associated with lung cancer in Canada. NSCLC represents approximately 85% of all cases of lung cancer and approximately 4% of patients with NSCLC are expected to have the ALK mutation. The standard first-line treatment for patients with ALK-mutation positive advanced NSCLC is crizotinib. For patients who have disease progression or intolerance to crizotinib, current treatment in the second-line setting includes ALK inhibitors (alectinib or ceritinib) and chemotherapy with platinum-based doublet therapy. Third-line options include single-agent chemotherapies (e.g., docetaxel, pemetrexed) or immunotherapies. pERC recognized that even though there are treatment options available for patients with ALK-positive NSCLC who progress on or are intolerant to crizotinib, there is a continued need for effective treatment options with more manageable toxicity profiles for these patients.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated two non-comparative, multi-centre, open-label, studies (ALTA, a phase II trial, and Study 101, a phase I/II trial) that investigated treatment with brigatinib in patients with advanced ALK-positive NSCLC who have progressed on crizotinib. pERC noted that ALTA provided the main evidence for the submission and was supplemented by a very small subgroup of patients from Study 101. pERC noted that patients in ALTA were randomized to receive either 90 mg brigatinib once daily (arm A) or 180 mg once daily (with a 7-day lead-in dosing of 90 mg) (arm B); however, no inferential comparison was conducted between the two arms. Only arm B was included in this appraisal, as the dose in arm A does not align with the Health Canada-approved dosing regimen. While pERC considered that ALTA and Study 101 were appropriately conducted non-randomized studies, the Committee noted that only limited conclusions could be drawn from these studies. Although pERC considered that the magnitude of objective tumour response observed with brigatinib in the two trials was important, pERC was concerned about the strength of the evidence due to the inherent biases of non-comparative studies, and reliance on tumour response as the principal measure of benefit. pERC noted that objective response rate (ORR) is an uncertain surrogate for survival in most solid tumours and that neither trial provided any comparative evidence on PFS, which has become the main deciding factor in treatment selection in the current era in which multiple targeted therapies for ALK inhibition are available. pERC agreed that the magnitude of effect of brigatinib compared with available therapies was uncertain given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, and QoL. In addition, pERC discussed that phase II trials are mainly hypothesis-generating and their intent is to determine whether or not there is sufficient promise to proceed to a phase III confirmatory trial. pERC noted that it is feasible to conduct a phase III RCT in this setting. Previous pCODR reviews in this line of therapy have been based on confirmatory phase III RCTs and there is an ongoing phase III trial with brigatinib in this patient population that may provide clarity on the comparative effectiveness of brigatinib in relation to a standard of care option (alectinib).

pERC discussed the available patient-reported outcomes data from ALTA and noted that the results suggested that brigatinib did not have a detrimental effect on QoL. However, the Committee noted that the number of patients providing QoL scores declined substantially over the course of the first year. pERC concluded that given the open-label design of the trial, the lack of a comparator group, and the insufficient follow-up time, there is considerable uncertainty in the QoL results.

pERC considered the safety of brigatinib and agreed with the Clinical Guidance Panel (CGP) that brigatinib's toxicity profile appeared manageable and consistent with the safety profile of common second-line ALK-inhibitor regimens. The most common treatment-emergent adverse events (TEAEs) included nausea, diarrhea, headache, and cough. The most common grade ≥ 3 TEAEs were hypertension, pneumonia, increased lipase, and increased blood creatine phosphokinase. However, pERC noted that the non-randomized design of ALTA makes interpreting the safety events attributable to brigatinib challenging, given that all patients received the same treatment.

Overall, pERC was not satisfied that there is a net clinical benefit to brigatinib compared with alectinib, ceritinib, or single-agent chemotherapy in the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib). While pERC was confident that brigatinib produces a tumour response, the Committee was unable to determine how brigatinib compares with other treatment options given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, and QoL. Given the availability of other treatments following progression on or intolerance to crizotinib, pERC was uncertain whether brigatinib addresses an unmet need. pERC reiterated that an ongoing randomized trial with brigatinib may provide clarity on the effectiveness of brigatinib compared with current treatment options in this setting.

pERC deliberated input from two patient advocacy groups. pERC noted that although few patient respondents had direct experience using brigatinib, they considered that patients value treatments that will delay disease progression, improve QoL, have manageable side effects, increase independence, can be administered at home, and lower the cost burden. Although the Committee acknowledged that brigatinib produces anti-tumour activity with manageable side effects, it was uncertain whether the current evidence demonstrates that brigatinib improves PFS, OS, or QoL compared with current treatment options. pERC considered that brigatinib is an oral treatment that could be administered at the patients' home and that patients value additional treatment options relevant to their genotype. pERC concluded that brigatinib aligned with patient values in that it produced anti-tumour activity, with manageable side effects, and offers an additional treatment choice. However, the Committee was unable to make conclusions on the benefit of brigatinib compared with other treatment options.

pERC deliberated the cost-effectiveness of brigatinib compared with alectinib, ceritinib, and single-agent chemotherapy. Because of the considerable limitations in the available clinical data of brigatinib from the non-comparative phase II studies and the lack of robust indirect comparative effectiveness estimates for PFS and OS, pERC concluded that it was not possible to draw meaningful conclusions on the cost-effectiveness of brigatinib. pERC noted that the submitter provided indirect treatment comparisons (ITCs) to present relative treatment effect estimates between comparators in the absence of head-to-head data. pERC agreed with the pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) that, given several limitations, including an unknown amount of bias in the unanchored effect estimates, the comparative effectiveness of brigatinib versus its comparators remains uncertain. The estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in the ALTA trial and the submitted ITCs translate into real and meaningful improvements in PFS and OS for brigatinib compared with other currently available therapies. However, given the limitations in the treatment effect estimates from the available phase II clinical trials and the ITC analyses, and the inability of the submitted economic model to account for the resulting uncertainty in the parameter estimates, pERC agreed that the clinical effectiveness estimates could not be used to inform credible incremental cost-effectiveness ratio (ICER) estimates. Therefore, pERC was unable to draw a conclusion on the cost-effectiveness and could not determine the ICERs for brigatinib compared with alectinib, ceritinib, or single-agent chemotherapy for the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib.

pERC considered the feasibility of implementing a reimbursement recommendation for brigatinib for the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. pERC discussed the Provincial Advisory Group's (PAG) request for clarity on sequencing of treatments, on whether treatment with brigatinib is appropriate in patients with intolerance to crizotinib, whether patients who do not tolerate second-line ceritinib could be switched to brigatinib, and on the appropriate definitions of disease progression and treatment discontinuation. pERC also considered that brigatinib is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. The budget impact was most sensitive to the proportion of patients who are ALK-positive and the duration of therapy. pERC noted that the key limitations of the budget impact analysis (BIA) are the unknown size of the patient population, the impact of alectinib in the first-line setting, and the market share of brigatinib.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and BIA
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups: Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA)
- Input from registered clinicians
- Input from pCODR's PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

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

Studies included: Two non-comparative studies, a phase II and phase I/II trial

The pCODR systematic review included two non-randomized trials: ALTA, a phase II trial (N = 222) and Study 101, a phase I/II trial (N = 137), which met the inclusion criteria for this review. Patients in ALTA 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). No statistical comparisons were planned between arms A and B with respect to efficacy or safety. Note that this pCODR review focused on the efficacy and safety results from arm B of ALTA, which is aligned with the Health Canada–approved dosing regimen of 180 mg (with the 90 mg lead-in). Regarding Study 101, only 18.2% of patients (25 out of 137) enrolled in Study 101 had been previously treated with crizotinib and received brigatinib, aligned with the current Health Canada–approved dosing regimen of 180 mg with a 7-day lead-in of 90 mg.

The ALTA study is an ongoing phase II clinical trial evaluating the efficacy and safety of brigatinib monotherapy for the treatment of ALK-positive NSCLC in patients who have progressed on crizotinib. 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). Patients were stratified based on baseline characteristics of presence of brain metastases and best-response to crizotinib (either complete response [CR] or partial response [PR]), as assessed by the investigator. No statistical comparisons were planned between arms A and B with respect to efficacy or safety.

All patients in arm B received the allocated dosing regimen. The median dose intensity for arm B was 174 mg per day.

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 2 or less. Patients were excluded based on the following key exclusion criteria: history or presence of pulmonary interstitial disease or drug-related pneumonitis, symptomatic central nervous system (CNS) metastases that were neurologically unstable or required an increasing dose of corticosteroids, any prior ALK inhibitor other than crizotinib, or crizotinib within three days of the first brigatinib dose.

Study 101 was a multiple-arm phase I/II dose-ranging trial. In phase I of this study, the dose for brigatinib was escalated with a starting dose of 30 mg up to a 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. Only 18.2% of patients (25 out of 137) enrolled in the study had been previously treated with crizotinib and received brigatinib, aligned with the current Health Canada–approved dosing regimen of 180 mg with a 7-day lead-in of 90 mg.

Patients were included in phase I of the study with histologically confirmed advanced malignancies other than leukemia. 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) epidermal growth factor receptor (EGFR) T790M-positive NSCLC and resistance to one previous EGFR tyrosine kinase inhibitor, (4) other cancers with abnormalities in brigatinib targets (e.g., 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 0 or 1.

Patient population: Median age 56 years; 73% of patients had prior platinum-based chemotherapy; 67.5% had brain metastases at baseline

Of the patients recruited into arm B (n = 110) of the ALTA trial, 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 patients. The ECOG PS 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. Any prior chemotherapy and, more specifically, prior platinum-based chemotherapy was received by 73.6% and 72.7% of patients in arm B, respectively.

For the subgroup 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 PS was 0 in 10 (40%) and 1 in 15 (60%) of the patients, with none of patients having a PS of 2. The majority of patients, 96%, had adenocarcinoma and had received prior chemotherapy (68%).

Key efficacy results: Important but uncertain response rates

The primary outcome measure for the ALTA trial was confirmed ORR by the investigator, per RECIST v.1.1. Secondary outcome measures were confirmed ORR as per independent review Committee (IRC), CNS response as IRC assessed ORR or PFS, duration of response, PFS, OS, safety, tolerability, patient-reported symptoms of lung cancer, and health-related QoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQ-30). The ORRs at the time of the first study report were 54% (97.5% confidence interval [CI], 43 to 65) in arm B. At the time of the February 21, 2017, data cut-off, the response was 55%; finally, for the last data analysis, the response was determined to be 56.4% (97.5% CI, 46.6 to 65.8) with complete response in five (4.5%) patients and partial response occurring in 57 (51.8%) patients. The investigator-assessed PFS in the initial study report for arm B was 12.9 months (95% CI, 11.1 to not reached [nr]). Longer-term estimates determined the PFS to be slightly longer at 15.6 months (95% CI, 11.1 to 21.0) based on the September 29, 2017, follow-up.

For patients in arm B of the ALTA trial, the one-year probability of survival was 80.1% (95% CI, 71 to 87) based on the September 29, 2017, data extraction; the two-year probability of survival was determined to be 66% (95% CI, 56 to 74). The median OS for arm B was 34.1 months (95% CI, 27.7 to nr) with 40 events (36.4%) in the 110 patients.

The analysis of the objective cranial response rates (OCRR) was stratified according to measurable and non-measurable brain metastases at baseline. Of the patients in arm B, 18 patients had measurable brain metastases. For these patients the confirmed OCRR was 66.7% (95% CI, 41.0 to 86.7) with no patients having a complete response. This rate remained constant across all analysis time points. 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 to 31) with 10 patients (18%) having a cranial complete response; this result remained constant across all analysis time points.

The primary outcome measure for the Study 101 trial in phase I was to establish the dose recommendations for the expansion phase. In the expansion phase, for the first four cohorts, the primary outcome was ORR by the investigator, per RECIST v.1.1. For cohort 5, a primary outcome of CNS response was used. Secondary outcome measures were ORR, 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). The ORR for the 25 patients enrolled in Study 101 was 80% (95% CI, 59.3 to 93.2) with 20 individuals responding to therapy. Of these responses to brigatinib, three (12%) were classified as complete response to therapy and 17 (68%) as partial responses based on the May 31, 2016, data cut-off. The median PFS 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 to 28.1). The estimated probability of PFS at the same data cut-off date was 62% (95% CI, 40 to 78).

The one-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 to 94) with a median OS (95% CI) of 29.5 months (95% CI, 21.4 to nr). The two-year OS probability was 64% (95% CI, 42 to 79).

Patient-reported outcomes: QoL results collected in the ALTA trial were uncertain

QoL was a secondary outcome in the ALTA trial using the EORTC-QLQ-30. Health-related QoL (HRQoL) was measured monthly, increased up to seven 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. In an evaluation of the ALTA trial, presented as an abstract form, 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 (five months on treatment) with 50% experiencing a clinically meaningful improvement. Multivariable mixed effects models were employed to assess adjusted mean changes from baseline. The number of patients providing QLQ-C30 scores declined to 43% (47 out of 110) at cycle 10 with an EORTC-QLQ-30 mean score (standard deviation) 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). The reduction in the number of respondents leads to uncertainty in the QoL results beyond one 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.

Safety: Manageable toxicity profile

The CGP noted that brigatinib has a toxicity profile that is manageable by clinicians and consistent with the safety profile of common second-line ALK-inhibitor regimens.

In the ALTA trial, arm B, all patients experienced at least one adverse event (AE). Seventy-two patients (65.5%) had a grade 3 severity or greater AE with serious 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% of patients secondary to a TEAE. The most common TEAEs in arm B were nausea (40%), diarrhea (38%), cough (34%), and headache (27%). The following grade 3 or greater TEAEs occurred (in 3% or more 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%).

A subset of pulmonary AEs with early onset occurred in 14 of 219 treated patients (all grades, 6%; grade 3 or higher, 3%) across arms A and B; none occurred after escalation to 180 mg in arm B. Fifty per cent of patients were successfully retreated with brigatinib.

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 one TEAE. Of these AEs, 20 patients (71.4%) had a grade 3 severity or greater AE with serious TEAEs 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% of patients secondary to a TEAE. The most commonly reported TEAEs 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 dyspnea (25%).

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 AE. The causes of these AEs were listed as neoplasm progression in eight patients (5.8%), and pneumonia, sudden death, hydrocephalus, and urosepsis in one patient (0.7%) each.

Limitations: No direct comparative data to ALK inhibitors (alectinib or ceritinib)

A manufacturer-submitted ITC that compared brigatinib with alectinib, ceritinib, chemotherapy, crizotinib re-treatment, and best supportive care for patients with ALK-positive NSCLC who progressed on crizotinib was summarized and critically appraised using the ISPOR Task Force Indirect

Comparison/Network Meta-analysis Study Questionnaire. The unanchored matching adjusted ITCs (MAICs) found that brigatinib statistically significantly improved PFS compared with ceritinib, alectinib, and chemotherapy, but no difference was found with crizotinib re-treatment. Brigatinib also statistically significantly improved OS compared with ceritinib and crizotinib re-treatment, but results were inconsistent when compared with alectinib and chemotherapy. Even though it was included in the ITC, crizotinib retreatment is not used in clinical practice. No difference was found when brigatinib was compared with ceritinib or chemotherapy for discontinuation due to AEs, and inconsistent results were seen when compared with alectinib. Brigatinib was associated with a lower likelihood of grade 3 or 4 AEs compared with alectinib; no difference was found when comparing brigatinib with ceritinib, and inconsistent results were seen when compared with chemotherapy. HRQoL 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 network meta-analysis (NMAs) is a serious limitation of the NMAs, along with the double-counting of patients on brigatinib, which resulted in falsely improved precision in the NMAs. Because of 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.

Need and burden of illness: Need for treatment that delays disease progression

In 2018, it was estimated that there were 28,600 new cases of lung cancer diagnosed, and 21,100 deaths associated with lung cancer in Canada. NSCLC represents approximately 85% of all cases of lung cancer and approximately 4% of patients with NSCLC are expected to have the ALK mutation. Standard first-line treatment for patients with ALK–mutation positive advanced NSCLC is crizotinib. For patients who have disease progression or intolerance to crizotinib, current treatment in the second-line setting includes ALK inhibitors (alectinib or ceritinib), and chemotherapy with platinum-based doublet therapy. Third-line options include single-agent chemotherapies (e.g., docetaxel, pemetrexed) or immunotherapies. pERC recognized that even though there are treatment options available for patients with ALK-positive NSCLC who progress on or are intolerant to crizotinib, there is a continued need for effective treatment options with more manageable toxicity profiles for these patients.

Registered clinician input: Brigatinib provides attractive treatment option; alectinib and ceritinib most relevant comparators; sequencing of alternative therapies remains unknown

pCODR received two group clinician inputs. 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 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 PFS than brigatinib. The clinicians from Cancer Care Ontario (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 choose alectinib as first-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.

PATIENT-BASED VALUES

Values of patients with ALK-positive NSCLC: Mutation-specific treatment option, delaying disease progression, improving QoL, manageable side effects, increased independence, treatment available at home, and lower cost burden

Two patient advocacy groups, Lung Cancer Canada (LCC) and the Ontario Lung Association (OLA), provided input to pCODR.

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 and 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 second-line treatment after progression on crizotinib include chemotherapy or chemoradiation, ceritinib, and alectinib. As reported by LCC, chemotherapy has many side effects that interfere with daily activities and 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 tumour 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 QoL. 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 patients' expectations included stopping or slowing the disease progression, reducing side effects, maintaining QoL, administration of treatments at home, and having less or no cost burden associated with the new treatment.

Patient values on treatment: Favourable experience; controlling cancer; manageable side effects; good QoL

LCC provided the perspective of five patients and four caregivers with experience with brigatinib. According to LCC, three key themes emerged from the patient experience with brigatinib: (1) it was effective in controlling cancer (including brain metastases), (2) it had manageable side effects, and (3) it allowed patients to have a good QoL. In particular, patients reported that brigatinib led to stable disease, reduced or eliminated brain metastases, helped overcome 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 pain. 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.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility (QALY) and cost-effectiveness (life-years) analyses

The EGP assessed one cost-utility analysis (clinical effects measured by QALYs gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of brigatinib compared with alectinib, ceritinib, or single-agent chemotherapy (pemetrexed) in adult patients with previously treated

ALK-positive metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib).

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, and utilities.

Costs considered in the analysis included those related to drug costs, administration cost (pemetrexed), disease management cost for all health states, AE costs, and end-of-life costs. Costs for subsequent lines of therapies were not included.

Drug costs: Treatment cost of brigatinib and comparators

- Brigatinib (oral) costs $112.32 per 30 mg or $336.96 per 90 mg or 180 mg.
  Dosage schedule: 90 mg orally once daily for the first seven days; if 90 mg is tolerated during the first seven days, the dose is increased to 180 mg orally once daily.
  Cost per 28-day cycle: $9,435.00.

- Alectinib (oral) costs $42.16 per 150 mg.
  Dosage schedule: 600 mg (four 150 mg capsules) given orally twice daily (total daily dose of 1,200 mg).
  Cost per 28-day cycle: $9,445.32.

- Ceritinib (oral) costs $52.00 per 150 mg.
  Dosage schedule: 750 mg (five 150 mg capsules) taken orally once daily.
  Cost per 28-day cycle: $7,280.00.

- Singe-agent chemotherapy (pemetrexed) (intravenous) costs $165.89 weekly.
  Dosage schedule: 500mg/m^2 every three weeks.
  Cost per 28–day cycle: $663.56.

Cost-effectiveness estimates: Substantial uncertainty in clinical effectiveness estimates

The submitter-provided economic analysis assessed the cost-effectiveness of brigatinib compared with alectinib, ceritinib, or single-agent chemotherapy (pemetrexed) in adult patients with previously treated ALK-positive metastatic NSCLC who have progressed on or who were intolerant to an ALK inhibitor (crizotinib).

pERC noted that the EGP's reanalyses of cost-effectiveness presented ICERs as lower bounds with no upper bounds, given the uncertainty around the clinical comparative efficacy of treatments. pERC also noted that the submitted base-case ICERs were lower than the EGP's lower-bound ICER estimates (submitted deterministic ICERs versus reanalyzed lower-bound deterministic ICERs: $37,733 versus $122,344 compared with alectinib and $64,285 versus $118,280 compared with ceritinib). This was primarily due to the following factors:

- OS data for alectinib (follow-up of 24 months instead of 6.9 months): Using updated, longer follow-up data changed the mean OS for alectinib from 18.8 months to 29.1 months, which in turn reduced the hazard ratio (HR) of brigatinib versus alectinib from 1.62 to 1.35.
- ITC analysis method (MAIC instead of NMA full MAIC fixed effect): The EGP used the following option for MAIC: pooled brigatinib data (ALTA plus Study 101) versus ALUR (alectinib) and ASCEND-5 (ceritinib and chemotherapy) data with a MAIC full analysis. While the unanchored MAIC had its own limitation, using the NMA would add additional limitations due to double-counting of patients on brigatinib and the fact that important covariates were not captured in all of the included studies in the MAIC comparisons. There were no statistical techniques to adjust for these limitations.
- Model of survival curves (gamma model instead of log-logistic model): The gamma model was selected for the OS survival model for brigatinib based on using a conservative approach to long-term modelling.
- Costs for AEs (changing the cost for non-major grade 3 and higher events to a specialist consultation and follow-up visit instead of hospitalization): The submitted model assumed in the base case that all grade 3 and higher AEs with brigatinib resulted in a hospital admission. Meanwhile, the European Medicines Agency reported that for patients treated with brigatinib, 49.7% of grade 3 and higher AEs resulted in a hospital admission. Thus, the EGP's reanalysis

estimated the average cost for non-major grade 3 and higher AEs, which were short in duration, to involve a specialist consultation and follow-up visit.
- Time on treatment (continue after progression instead of capped by PFS): The EGP selected the time on treatment to continue for 1.54 months after radiological disease progression, based on CGP opinion.

The EGP noted several limitations in the submitted analysis, particularly the uncertainty in the clinical comparative efficacy data. The submitter provided ITCs to present relative treatment effect estimates between comparators in the absence of head-to-head data. The pCODR Methods Team and the EGP agreed that, given several limitations, including an unknown amount of bias in the unanchored effect estimates, the comparative effectiveness of brigatinib versus its comparators remained uncertain (for more details on the ITCs, see paragraph on "limitations"). The estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in the ALTA trial and the submitted ITCs translate into real and meaningful improvements in PFS and OS for brigatinib compared with other currently available therapies. However, given the limitations in the treatment effect estimates from the available phase II clinical trials and the ITC analyses, and the inability of the economic model to account for the resulting uncertainty in the parameter estimates, the EGP's reanalyzed ICER estimates were uncertain and the EGP elected to place no upper bounds on its best-case ICER estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

pERC considered the feasibility of implementing a reimbursement recommendation for brigatinib for the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib. PAG requested clarity on whether data is available for the comparison of brigatinib with alectinib and ceritinib, on the use of brigatinib following first-line treatment with alectinib, and whether the one week dose escalation phase could lead to dosing errors and patient confusion. PAG also noted that there may be a potential for drug wastage for dose adjustments from 180 mg back to 90 mg daily. pERC also considered that brigatinib is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. The budget impact was most sensitive to the proportion of patients who are ALK-positive and the duration of therapy. pERC noted that the key limitations of the BIA are the unknown size of the patient population, the impact of alectinib in the first-line setting, and the market share of brigatinib.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Anil Abraham Joy and Dr. Kelvin Chan, who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of brigatinib for non-small cell lung cancer, through their declarations, none of the members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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