pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Brigatinib (Alunbrig)

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

Submitted By: Takeda Canada Inc.	**Manufactured By:** Takeda Canada Inc.
NOC Date: March 3, 2021	**Submission Date:** September 30, 2020
Initial Recommendation: April 1, 2021	**Final Recommendation:** April 21, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	Brigatinib costs $336.96 per 90 mg tablet and per 180 mg tablet. At the recommended dose of 90 mg orally once daily for 7 days, then 180 mg orally once daily continuously, brigatinib costs $9,434.88 per 28-day cycle.

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 conditionally recommends reimbursement of brigatinib for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- the public drug plan costs of treatment with brigatinib should not exceed the public drug plan price of alectinib, which is currently reimbursed for ALK inhibitor-naïve locally advanced or metastatic NSCLC.

Eligible patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity, whichever occurs first.

pERC made this recommendation because it was satisfied that there is a net clinical benefit with brigatinib compared with crizotinib based on statistically significant and clinically meaningful improvements in progression-free survival (PFS), clinically meaningful improvements in intracranial response and intracranial PFS in patients with baseline central nervous system (CNS) metastases, a manageable toxicity profile, and maintenance of quality of life (QoL). However, given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of brigatinib compared with alectinib, the relevant treatment option.

	The Committee also concluded that brigatinib aligns with the following patient values: offers symptom and disease control in patients with CNS metastases, improves disease symptoms, delays disease progression, offers long-lasting durable treatment, maintains QoL, has manageable side effects, and offers an additional treatment option with a convenient oral route of administration. pERC concluded that brigatinib was not cost-effective at the submitted price in comparison with crizotinib. pERC was unable to conclude on the cost-effectiveness of brigatinib versus alectinib, given the limitations with the indirect treatment comparison. The estimates were sensitive to assumptions about comparative effectiveness of brigatinib to alectinib, and about treatment duration. CADTH's reanalysis of the sponsor's budget impact analysis suggests that the budget impact of introducing brigatinib to the market is relatively small but was underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of brigatinib compared with crizotinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of brigatinib. pERC noted that a reduction in the price of brigatinib would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In Canada, it was estimated that 29,800 people will be diagnosed with lung cancer and 21,200 people will die of the disease in 2020. Non-small cell lung cancer represents approximately 85% of all cases of lung cancer. The majority of patients are diagnosed with advanced disease and the 5-year relative overall survival (OS) rate of patients with NSCLC has been estimated to be 25%. In Canada, approximately 2.5% of non-squamous NSCLC patients are ALK-positive. Central nervous system metastases are common in ALK-positive lung cancers, seen in up to 30% of patients at diagnosis and developing in more than 50% of patients who were initially treated with crizotinib. In 2018, alectinib received a positive conditional pERC recommendation as first-line treatment for patients with ALK-positive, locally advanced or metastatic NSCLC. Alectinib has supplanted crizotinib as standard of care and is the preferred first-line ALK inhibitor. Alectinib is currently funded in most provinces. pERC agreed with the CADTH Clinical Guidance Panel (CGP) that novel therapies that further improve survival, are effective in the management of CNS metastases, and provide an additional treatment choice are a continued need 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 on the results of one randomized, multinational, open-label, phase III trial (ALTA-1L) that evaluated the efficacy and safety of brigatinib compared with crizotinib in patients with advanced ALK-positive NSCLC who have not previously received an ALK inhibitor. pERC considered that PFS, the primary outcome of the trial, was statistically significant and clinically meaningful in favour of brigatinib. Key secondary outcomes, though not statistically significant, showed a marked and clinically meaningful trend toward improvement in intracranial response and intracranial PFS in patients with CNS metastases at baseline. pERC noted that the results for OS (a key secondary outcome) are immature at present (median OS was not reached in either treatment group) and may be confounded by a high rate of crossover from the crizotinib group to the brigatinib group. In the absence of OS data, pERC discussed the clinical meaningfulness of PFS in the ALK-positive NSCLC setting. pERC agreed with the CGP and the registered clinicians providing input to this submission that PFS is an established outcome in guiding treatment selection in this setting. Delaying disease progression and reducing CNS metastases are clinically relevant outcomes as these events are associated with higher burden of symptoms, decrease in QoL, and shorter survival times. Overall, pERC agreed that the improvements in PFS observed in the trial are of clinical importance for patients with this incurable disease.

pERC deliberated on the safety of brigatinib and noted that almost all patients in the trial experienced at least one any-grade treatment-emergent adverse event (TEAE). Those any-grade TEAEs occurring more frequently in the brigatinib group included increased blood creatine phosphokinase, cough, hypertension, and pruritus. Any-grade TEAEs occurring more frequently in the crizotinib group included peripheral edema, nausea, constipation, and vomiting. pERC noted that more grade 3 or higher adverse events (AEs) occurred in the brigatinib group mostly attributable to increased blood creatine phosphokinase. While TEAEs requiring treatment interruptions and dose reductions were higher in the brigatinib group, treatment discontinuation as a consequence was relatively rare. Overall, pERC agreed with the CGP as well as with the registered clinicians providing input that brigatinib's toxicity profile was acceptable and manageable.

pERC members discussed the available patient-reported outcomes data from the ALTA-1L trial and noted that the results suggested a trend for greater improvements in the brigatinib group compared with the crizotinib group and that brigatinib appeared to delay time to deterioration compared with crizotinib. However, given the open-label design of the trial, the exploratory nature of the analyses, and the gradually declining number of patients providing assessments over time, pERC noted that there was uncertainty in the results. It was also noted that the assessment of time-to-deterioration in dyspnea was challenging to interpret as this analysis was included as a protocol amendment and did not capture the experience of all patients in the trial. The Committee concluded that, overall, brigatinib appeared to maintain QoL compared with crizotinib.

pERC also noted that while the ALTA-1L trial compared brigatinib with crizotinib, alectinib is currently the standard of care and the preferred first-line ALK inhibitor in clinical practice in Canada. Both crizotinib and alectinib are currently funded in most provinces. In the absence of a direct comparison of brigatinib with alectinib, pERC considered sponsor-provided indirect treatment comparisons (ITCs) comparing the efficacy of brigatinib with alectinib. pERC noted that the results of the ITCs suggested no difference between brigatinib and alectinib for OS, objective response rate (ORR), PFS, and duration of response (DOR). Additionally, pERC noted that the CADTH Methods Team had identified 2 published ITCs that similarly suggested that there was no difference between brigatinib and alectinib for OS and PFS. However, pERC acknowledged the limitations noted by the CADTH Methods Team and agreed with their concerns regarding heterogeneity across the study designs and populations, and the inability to adjust for all potential confounders and prognostic variables in the matching-adjusted indirect comparison (MAIC). Therefore, pERC agreed with the CGP and CADTH Methods Team's conclusion that the magnitude of the uncertainty in the analyses precluded drawing definitive conclusions about the comparative effectiveness of brigatinib versus alectinib.

In summary, pERC concluded that compared with crizotinib, there is a net clinical benefit of brigatinib based on statistically significant and clinically meaningful improvements in PFS, clinically meaningful improvements in intracranial response and intracranial PFS in patients with baseline CNS metastases, a manageable toxicity profile, and maintenance of QoL. However, given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of brigatinib compared with alectinib, the relevant treatment option.

pERC deliberated on the patient advocacy group input from one patient group concerning brigatinib and noted that key concerns with ALK-positive NSCLC included the aggressiveness of the disease with low survival rates and the presence of brain metastases, that have debilitating effects on the patient and result in poorer prognosis and survival. The patient group also emphasized the unmet need for therapeutic options that are effective in treating both systemic disease and CNS metastases to reduce the need other treatments that have negative cognitive side effects. A few patients who had direct experience using brigatinib indicated that brigatinib had controlled their cancer, was effective in treating systemic and CNS disease, reduced the size of their tumours, and allowed them to live a productive and fulfilling life. The durability of treatment with brigatinib while maintaining good QoL was also highlighted by the patient group. Common side effects experienced with brigatinib included fatigue, vomiting, diarrhea, constipation, abdominal pain, and muscle and joint pain. pERC agreed that the benefits of brigatinib outweighed the potential risk of side effects and concluded that the use of brigatinib aligned with the following patient values: offers symptom and disease control in patients with CNS metastases, improves disease symptoms, delays disease progression, offers long-lasting durable treatment, maintains QoL, has manageable side effects, and offers an additional treatment option with a convenient oral route of administration. However, pERC noted that in some jurisdictions, oral medications are not funded by the same mechanism as intravenous cancer medications.

pERC deliberated on the cost-effectiveness of brigatinib compared to comparator treatments alectinib and crizotinib. Because of the identified shortcomings in the sponsor's MAIC, the estimates of incremental efficacy were informed by estimates from a literature-published network meta-analysis (NMA). pERC noted that while the pharmacoeconomic analysis using the NMA-based estimates produced a result suggesting that brigatinib was dominated by alectinib (brigatinib was more costly and less effective), the available evidence was not sufficiently robust to support a conclusion that brigatinib is inferior. pERC concluded that given the high uncertainty in comparative clinical effectiveness of brigatinib compared to alectinib the price of brigatinib should not exceed the price of alectinib. pERC also noted that both the available evidence and the sponsor's pharmacoeconomic model were limited in their abilities to characterize time-on-treatment for alectinib. These limitations contributed uncertainty to the size of the price reduction necessary for brigatinib to be no more expensive than alectinib.

pERC also discussed the budget impact analysis and noted that the sponsor's base case was likely an underestimate. Given the small population and the presence of another effective funded comparator, pERC noted that the anticipated budgetary impact was likely small and would be smaller in the presence of an appropriate price reduction.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Lung Cancer Canada [LCC])
- input from two registered joint clinician inputs: 3 clinicians from Ontario Health Cancer Care Ontario (CCO) and 13 clinicians from LCC
- input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, LLC
- Two clinician groups, LLC and Ontario Health CCO
- The PAG
- The sponsor, Takeda Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of brigatinib for the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an ALK inhibitor if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- the public drug plan costs of treatment with brigatinib should not exceed the public drug plan price of alectinib, which is currently reimbursed for ALK inhibitor–naïve locally advanced or metastatic NSCLC.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group, registered clinician groups, the PAG, and the sponsor agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

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

Studies included: One ongoing, multinational, randomized phase III trial (ALTA-1L)

The CADTH systematic review included one randomized controlled trial (RCT) (ALTA-1L) that assessed the efficacy and safety of brigatinib compared to crizotinib for patients with advanced ALK-positive NSCLC who had not previously received an ALK inhibitor.

A total of 275 patients were randomized in a 1:1 ratio to receive brigatinib (N = 137) or crizotinib (N = 138). Randomization was stratified by the presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease. Patients randomized to brigatinib received a 90 mg oral dose once daily for 7 days, then 180 mg orally once daily continuously. Patients randomized to crizotinib received an oral 250 mg dose twice daily. After experiencing progressive disease, patients in the brigatinib group could continue the study treatment if they continued to experience clinical benefit in the opinion of the investigator, and patients in the crizotinib group could crossover from crizotinib to brigatinib at the investigator's discretion.

Median time on randomized study treatment was 24.3 months in the brigatinib group and 8.4 months in the crizotinib group. Median dose intensity was 163.83 mg/day in the brigatinib group and 495.64 mg/day

in the crizotinib group. Median relative dose intensity was 96.89% in the brigatinib group and 99.12% in the crizotinib group.

Eligible patients had stage IIIB/IV ALK-positive NSCLC, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, were previously untreated with an ALK inhibitor, received no more than one systemic chemotherapy regimen, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. Brain metastases at baseline were allowed if they were asymptomatic. Patients who had previous treatment with an investigational anticancer drug, a tyrosine kinase inhibitor (TKI), or more than one regimen of systemic anticancer therapy were excluded.

Patient populations: Median age 59 years, baseline characteristics well balanced

Overall, the distributions of baseline characteristics between the treatment groups were well balanced. The median age of patients was 59 years old, with a range of 27 to 89 years. Most patients were female (55%), of non-Asian race (61%), had never smoked (58%), and had an ECOG performance status of 0 or 1 (96%). Most of the non-Asian patients were White (97%). Most patients had metastatic disease (93%) and adenocarcinoma histological type (96%). Overall, 27% (n = 81) of patients had received previous chemotherapy, including adjuvant chemotherapy (7%), neoadjuvant chemotherapy (3%), chemotherapy for advanced or metastatic disease (22%), and other chemotherapy (1%), at study entry. Approximately 27% of patients had prior radiation therapy (24% in the brigatinib group and 29% in the crizotinib group). Brain metastases were present in 29% of patients at baseline as assessed by the investigator. Approximately 13% of patients had received radiotherapy to the brain.

Key efficacy results: Statistically significant improvement in PFS in favour of brigatinib

The primary outcome of the ALTA-1L trial was PFS as assessed by a blinded independent review committee (BIRC). Key secondary outcomes were confirmed ORR by BIRC, intracranial ORR by BIRC, intracranial PFS by BIRC, and OS. Additional secondary outcomes included DOR by BIRC, disease control rate by BIRC, patient-reported outcomes, and safety.

At the first interim analysis (data cut-off date February 19, 2018), median follow-up times for patients in the brigatinib and crizotinib groups were 11.0 months and 9.3 months, respectively. Median BIRC-assessed PFS was not reached (NR) in the brigatinib group versus 9.8 (95% confidence interval [CI], 9.0 to 12.9 months) months in the crizotinib group. Brigatinib was associated with a statistically significant improvement in BIRC-assessed PFS compared to crizotinib (hazard ratio [HR] = 0.49; 95% CI, 0.33 to 0.74; P < 0.001).

The ORR confirmed by the BIRC was 71% (95% CI, 62% to 78%) in the brigatinib group versus 60% (95% CI, 51% to 68%) in the crizotinib group (odds ratio [OR] = 1.59; 95% CI, 0.96 to 2.62; P = 0.0678). Although the results suggested a trend in favour of brigatinib, they were not statistically significant (P = 0.0678). Median DOR was NR (95% CI, NR to NR) in the brigatinib group versus 11.1 (95% CI, 9.2 to NR) months in the crizotinib group.

Confirmed intracranial ORR in patients with any brain metastases at baseline was 67% (N = 29) in the brigatinib group compared to 17% (N = 8) in the crizotinib group (OR, 13.00; 95% CI, 4.38 – 38.61). Median intracranial PFS in the intention-to-treat (ITT) population was NR (95% CI, NR – NR) in the brigatinib group versus NR (95% CI, 11.07 – NR) in the crizotinib group (HR, 0.415; 95% CI, 0.24 – 0.70).

The OS data were immature and median OS was NR in both treatment groups. As of the first interim analysis, 12% (N = 17) of patients in the brigatinib group and 12% (N = 17) of patients in the crizotinib group had died.

At the second interim analysis (data cut-off date July 28, 2019), median follow-up times for patients in the brigatinib and crizotinib groups were 24.9 months and 15.2 months, respectively. Median BIRC-assessed PFS was 24.0 months [95% CI, 18.5 – NR] in the brigatinib group versus 11.0 months (95% CI, 9.2 – 12.9 months) with crizotinib. Consistent with the first interim analysis, brigatinib was associated with an improvement in PFS as compared to crizotinib (HR, 0.49; 95% CI, 0.35 – 0.68).

The ORR confirmed by the BIRC was 74% (95% CI, 66 – 81%) in the brigatinib group versus 62% (95% CI, 53 – 70%) in the crizotinib group (OR, 1.73; 95% CI, 1.04 – 2.88). Median DOR was NR in the brigatinib group (95% CI, 19.4 months – NR) versus 13.8 months (95% CI, 9.3 – 20.8 months) in the crizotinib group.

Confirmed intracranial ORR in patients with any brain metastases at baseline was 66% (95% CI, 51 – 70%) in the brigatinib group versus 16% (95% CI, 7 – 30%) in the crizotinib group (OR, 11.75; 95% CI, 4.19 – 32.91). Median intracranial PFS in the ITT population was 32.3 months (95% CI, 29.5 months – NR) in the brigatinib group compared to 24.0 months (95% CI, 12.9 months – NR) in the crizotinib group (HR, 0.45; 95% CI, 0.29 – 0.69).

The OS data were immature and median OS was NR in both treatment groups. As of the second interim analysis, 70 deaths were reported: 33 (24%) patients in the brigatinib group had died versus 37 (27%) patients in the crizotinib group.

Patient-reported outcomes: Overall brigatinib maintained QoL compared with crizotinib

In the ALTA-1L trial patient-reported outcomes data were collected using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3.0), and the EORTC lung cancer-specific module (QLQ-LC13, version 3.0). The EORTC QLQ-LC13 was added to the ALTA-1L trial in protocol amendment 1, and only patients enrolled after the protocol amendment were included in the analysis. Questionnaires were administered at day 1 of every 4-week cycle during treatment, at the end of treatment, and 30 days after the last dose. The patient-reported outcomes analyses were not included in the testing hierarchy, and therefore, no adjustments were made for type I error.

As of the second interim analysis, overall compliance with EORTC QLQ-C30 across all time points was 98% in the brigatinib group and 97% in the crizotinib group. Based on the least square mean difference in change from baseline in the EORTC QLQ-C30 global health status quality of life (GHS/QoL) scale, there was a trend for greater improvements in the brigatinib group compared with the crizotinib group with an overall change from baseline in between-group mean difference of 3.1 (95% CI, –0.8 to 7.0). Brigatinib also showed trends toward improvements compared with crizotinib in most functional and symptom subscales of the EORTC QLQ-C30 instrument. Forty-four percent (n = 57) of patients in the brigatinib group and 53% (n = 70) of patients in the crizotinib group had a deterioration in GHS/QoL score of 10 points or more. Results of the GHS/QoL score suggested that brigatinib delayed median time to worsening event compared with crizotinib; median time to worsening was 26.7 (95% CI, 8.3 to NR) months and 8.3 (95% CI, 5.7 to 13.5) months in the brigatinib and crizotinib groups, respectively (HR = 0.70; 95% CI, 0.49 to 1.00; P = 0.049). As well, brigatinib delayed time to worsening compared with crizotinib across most EORTC QLQ-C30 subscale scores. As of the second interim analysis, 60% (n = 79) of patients in the brigatinib group and 63% (n = 83) of patients in the crizotinib group showed an improvement of 10 points or more in GHS/QoL score. In patients that demonstrated improvement in GHS/QoL score, the median duration of improvement was NR in the brigatinib group compared to 12.0 (95% CI, 7.7 to 17.5) months in the crizotinib group (HR = 0.27; 95% CI, 0.14 to 0.49; P < 0.0001).

A total of 141 (51%) patients were included in the EORTC QLQ-LC13 analysis (63 [46%] patients in the brigatinib group and 78 [57%] patients in the crizotinib group). The overall compliance was 98% in the brigatinib group and 95% in the crizotinib group. The percentage of patients that experienced worsening dyspnea (defined as a 50% decline from baseline) was higher in the crizotinib group compared with the brigatinib group; 22% in the brigatinib group and 33% in the crizotinib group (HR = 0.54; 95% CI, 0.28 to 1.04; P = 0.0658). The median time to worsening in dyspnea was prolonged in the brigatinib group compared with the crizotinib group (HR = 0.54; 95% CI, 0.28 to 1.04).

Due to the open-label design of the trial, the exploratory nature of the analyses, and the gradually declining number of patients providing assessments over time, there was uncertainty in the results. The assessment of time-to-deterioration in dyspnea was challenging to interpret as this analysis was included as a protocol amendment and did not capture the experience of all patients in the trial.

Limitations: No direct comparative data to alectinib

The CADTH Methods Team summarized and critically appraised sponsor-provided ITCs comparing the efficacy of brigatinib with alectinib and ceritinib. Ceritinib is currently not a relevant comparator for this review as it is not a funded option and has not been reviewed by pERC for this indication. pERC noted that the results of the ITCs suggested no difference between brigatinib and alectinib for OS, ORR, PFS, and

DOR. Additionally, pERC noted that the CADTH Methods Team had identified 2 published ITCs (Elliott et al. [2020] and Ando et al. [2020]), which similarly suggested that there was no difference between brigatinib and alectinib for OS (Ando et al. did not report on OS) and PFS. The ITC by Ando et al. (2020) suggested in addition no difference for grade 3 to 5 AEs between brigatinib and alectinib.

The CADTH Methods Team identified several limitations with the sponsor-provided ITCs including concerns regarding: heterogeneity across the study designs and populations, the inability to adjust for all potential confounders and prognostic variables in the MAIC, and that analyses were performed by a consultancy group hired by the sponsor which introduced the potential for a conflict of interest. Limitations identified with the published ITCs included concerns regarding: dearth of RCTs available on ALK inhibitors for NSCLC, and heterogeneity across study populations and designs that could not be adjusted for due to lack of individual patient data. The CADTH Methods Team concluded that due to several limitations identified in the ITCs, there is uncertainty with respect to the comparative effectiveness of brigatinib versus alectinib.

Safety: Manageable toxicity profile

Overall, 99.6% of patients in the overall trial population experienced an any-grade TEAE. The most frequently reported any-grade TEAEs (brigatinib versus crizotinib) were diarrhea (52% versus 56%), nausea (30% versus 58%), and increased blood creatine phosphokinase (46% versus 17%). Any-grade TEAEs occurring more frequently in the brigatinib group included (brigatinib versus crizotinib) increased blood creatine phosphokinase (46% versus 17%), cough (35% versus 20%), hypertension (32% versus 8%), and pruritus (18% versus 5%). Any-grade TEAEs occurring more frequently in the crizotinib group included (brigatinib versus crizotinib) peripheral edema (7% versus 45%), nausea (30% versus 58%), constipation (18% versus 42%), and vomiting (21% versus 44%).

A greater proportion of patients in the brigatinib group experienced a grade 3 or greater AE compared to the crizotinib group (73% versus 61%, respectively). The most commonly reported grade 3 or greater AEs in the brigatinib group were increased blood creatine phosphokinase (24%), increased lipase (14%), and hypertension (12%). In the crizotinib group, the most commonly reported grade 3 or greater AEs were increased alanine aminotransferase (10%), increased aspartate aminotransferase (7%), and increased lipase (7%).

There were more events of interstitial lung disease and pneumonitis (early onset and late onset) in the brigatinib group (n = 4; 3%) than in the crizotinib group (n = 1; 1%). Early onset interstitial lung disease/pneumonitis occurred in 5 brigatinib-treated patients: 4 patients (2.9%) from the brigatinib group in the randomized phase and one patient (1.6%) from the crizotinib group in the crossover phase.

Dose interruptions due to AEs occurred in 66% of patients in the brigatinib group and 47% of patients in the crizotinib group. Dose reductions due to AEs occurred in 38% of treated patients in the brigatinib group and 25% of patients in the crizotinib group. The number of patients with AEs leading to study drug discontinuation were 12.5% and 9% in the brigatinib and crizotinib groups, respectively. During the period of randomized treatment and survival follow-up, 24% of patients in the brigatinib group and 18% of patients in crizotinib group died. The most common reason for death was cancer-related (20% and 14% in the brigatinib and crizotinib groups, respectively). Adverse events resulting in death within 30 days of the last study drug dose occurred in 7% (n = 9) of patients in the brigatinib and 7% (n = 10) of patients in the crizotinib group. All AEs resulting in death were assessed as unrelated to the study drug.

Need and burden of illness: Continued need for effective novel therapies

In Canada, it was estimated that 29,800 people will be diagnosed with lung cancer and 21,200 people will die of the disease in 2020. Non-small cell lung cancer represents approximately 85% of all cases of lung cancer. The majority of patients are diagnosed with advanced disease and the 5-year relative OS rate of patients with NSCLC has been estimated to be 25%. In Canada, approximately 2.5% of non-squamous NSCLC patients are ALK-positive. CNS metastases are common in ALK-positive lung cancers, seen in up to 30% of patients at diagnosis and developing in more than 50% of patients who were initially treated with crizotinib. In 2018, alectinib received a positive conditional pERC recommendation as first-line treatment for patients with ALK-positive, locally advanced or metastatic NSCLC. Alectinib has supplanted crizotinib as standard of care and is the preferred first-line ALK inhibitor. Alectinib is currently funded in most provinces. Novel therapies that further improve survival, are effective in the management of CNS metastases, and provide an additional treatment choice are a continued need for these patients.

Registered clinician input: Brigatinib is an additional treatment option

Registered clinician input was provided by two clinician groups: 3 clinicians from Ontario Health CCO and 13 clinicians from LCC. Both clinician groups indicated that the most appropriate comparator in the first-line setting is alectinib and that they would prescribe brigatinib to patients with advanced ALK-positive NSCLC in the first-line setting. Clinicians from CCO, stated that because alectinib is already used in the first line, brigatinib would be an additional option, and there is not an unmet need. In contrast, clinicians from LCC indicated that there is a significant unmet need for additional ALK-targeting drugs in all lines of therapy, including first line. In the event that alectinib is not available, it would be beneficial to have another option. All clinicians had experience using brigatinib. Clinicians from LCC stated that given the prevalent and established use of alectinib in the first-line setting, and its dominance over early generation ALK TKIs such as crizotinib and ceritinib, brigatinib will likely be used in the first-line setting under specific circumstances when an alternative is preferred or required (i.e., toxicity by alectinib). The selection of brigatinib as a first line therapy may be preferred due to its efficacy in treating brain metastases at baseline. Brigatinib may have more grade 3 toxicities than alectinib. The difference appears mostly related to deranged biochemical parameters with uncertain clinical effects, which can lead to higher rates of dose interruptions and dose reductions. Brigatinib has similar low toxicity-related treatment discontinuation rates as alectinib. According to clinicians, both drugs are well tolerated by patients. Both clinician groups stated that ALK testing has been standardized in Canada and as a result, jurisdictions across Canada have uniformly adopted its use in routine lung biomarker testing.

PATIENT-BASED VALUES

Values of patients with ALK-positive NSCLC: Aggressive disease with low survival rates and debilitating effects from brain metastases

One patient group, LCC, provided input on brigatinib for ALK-positive NSCLC. According to the input received, key concerns with ALK-positive NSCLC included the aggressiveness of the disease with low survival rates and the presence of brain metastases that have debilitating effects on the patient and result in poorer prognosis and survival. The patient group also emphasized the unmet need for therapeutic options that are effective in treating both systemic disease and CNS metastases to reduce the need for other treatments that have negative cognitive side effects. According to the input received, common therapies for ALK-positive NSCLC include crizotinib and alectinib and allow patients to be functional and active, have a good QoL, live longer, and improve their prognosis and survival rates. Reported side effects of crizotinib were nausea, vomiting, diarrhea, visual disturbances, edema, and fatigue. Some patients did find the side effects intolerable. It was noted that alectinib appears to have better efficacy and lower toxicity compared to crizotinib. Alectinib has been found to be effective in treating patients with brain metastases, thus reducing or eliminating the need for whole brain radiation. Alectinib is generally very well tolerated with manageable side effects.

Patient values on or expectations for treatment: Effective at treating CNS metastases, improved symptoms and OS, good QoL, manageable side effects, long-lasting treatment, delay in disease progression, and additional treatment options with an oral rout of administration

Two patients reported having experience with brigatinib as first-line treatment for ALK-positive NSCLC. Brigatinib controlled the cancer, reduced the size of tumours, and enabled patients to live a productive and fulfilling life. Common side effects reported by respondents included fatigue, vomiting, diarrhea, constipation, abdominal pain, and muscle and joint pain. The durability of treatment with brigatinib while maintaining a good QoL was also highlighted by the patient group. Overall, patients valued new treatments for ALK-positive NSCLC that will be effective at treating CNS metastases, improve symptoms and OS, offer good QoL, have manageable side effects, enable long-lasting treatment, delay disease progression, and offer an additional treatment option with an oral route of administration.

ECONOMIC EVALUATION

Economic Evaluation

Brigatinib is available as 90 mg and 180 mg tablets. The recommended dosing of brigatinib is 90 mg daily for the first 7 days and, if 90 mg is tolerated during the first 7 days, the dose is increased to 180 mg daily

for subsequent months. Treatment with brigatinib should be continued until disease progression or unacceptable toxicity occurs. At the sponsor's submitted prices of $336.96 per tablet regardless of strength, the daily drug acquisition cost is $336.96 or $9,434.88 for a 28-day cycle.

The sponsor submitted a cost-utility analysis of brigatinib compared with crizotinib and alectinib in adults (≥ 18 years) with locally advanced or metastatic ALK-positive NSCLC (i.e., per the reimbursement request). The sponsor's partitioned survival model consisted of 4 health states: PFS (time from randomization to the date of the BIRC's first documentation of progressed tumour per the RECIST v1.1 criteria; of radiotherapy for brain metastasis; or of death from any cause); CNS Progression; non-CNS progression; and death. Time spent in each state was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis (30 years) using parametric methods. All patients entered the model in the PFS health state and were assumed to be on treatment for the full duration of time spent in this state. Patients who progressed were assumed to stop first-line treatment. The data used to characterize CNS-PFS, PFS, and OS for the brigatinib and crizotinib comparators were obtained from the ALTA-1L trial. To model PFS and OS for alectinib, data were obtained from a sponsor-conducted unanchored MAIC of the ALTA-1L, ALEX, and ASCEND-4 trials. For each comparator within the model, duration of treatment was assumed to be equal to PFS.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The sponsor's base case assumed duration on treatment (DoT) was equal to PFS for each treatment. Trial-observed DoT for each comparator and feedback from clinical experts consulted by CADTH indicated that patients would continue to receive treatment after progression in many cases, and that PFS therefore underestimates DoT.
- The sponsor incorporated treatment-specific utilities, which does not reflect CADTH guidelines.
- The CADTH Clinical Review identified several limitations with the sponsor's unanchored MAIC between brigatinib and alectinib and concluded that internal validity of these results was low.

CADTH reanalyses included estimating DoT for brigatinib by extrapolating time-on-treatment data from the ALTA-1L study data, using non-treatment-specific utility weights provided by the sponsor for each health state, and deriving OS and PFS curves from a published NMA rather than the sponsor's submitted unanchored MAIC. According to the sequential analysis of the CADTH base case, the incremental cost-effectiveness ratio for brigatinib was dominated by alectinib (i.e., more costly, less effective). The probability that brigatinib represented the most cost-effective strategy was 0% at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year. An exploratory analysis conducted using the CADTH base case suggested that a 46% price reduction was necessary for brigatinib to be equivalent in cost to alectinib.

The CADTH reanalysis is subject to considerable uncertainty. While CADTH was able to adjust DoT data for brigatinib, there was no data to inform such adjustment for alectinib; this discrepancy informs much of the incremental costs found within CADTH's reanalysis. The CADTH Clinical Review noted that while the NMA was a more appropriate source of OS and PFS data than the sponsor's unanchored MAIC, the NMA estimates are still subject to methodological limitations and that the estimate of incremental effectiveness should be interpreted with caution. pERC concluded that the clinical effectiveness of brigatinib is greater than crizotinib, and likely comparable to alectinib. Due to the described limitations within the submitted evidence, the cost-effectiveness of brigatinib compared to alectinib remains highly uncertain.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Low Impact

The sponsor's estimate of market share for brigatinib was underestimated, as was the eligible population size. CADTH's reanalysis estimated an annual budget impact ranging between $1,491,797 and $4,231,705.

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
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, 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. Maureen Trudeau, who did not vote due to her role as Committee chair.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of brigatinib for ALK-positive NSCLC, through their declarations, no members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were 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 CADTH 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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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC Recommendation
Eligible patient population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with brigatinib:	
• patients who previously received more than one systemic anticancer therapy regimen for advanced disease	• Patients were eligible to enter the ALTA-1L trial if they had received no more than one prior systemic anticancer therapy regimen for locally advanced or metastatic disease. Overall, 27% of patients had received previous chemotherapy. Of these patients, the majority had received chemotherapy for advanced or metastatic disease and few patients had received neoadjuvant and/or adjuvant chemotherapy. pERC noted that in exploratory analyses, the benefit of treatment with brigatinib was seen in patients regardless of whether they had received one prior line of chemotherapy or not and agreed with the CGP that it would be reasonable to generalize the results to patients who have received more than one line of previous chemotherapy for locally advanced or metastatic disease. However, pERC agreed with the CGP that patients should not have previously been treated with an ALK inhibitor such as crizotinib or alectinib.
• patients who received chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days before the first dose of brigatinib	• The ALTA-1L trial limited trial eligibility to patients who had not received chemotherapy or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within 14 days of the first dose of study drug. pERC and the CGP agreed with the trial eligibility criteria and noted there is insufficient evidence to offer brigatinib to patients who had received chemotherapy or radiation therapy within 14 days before the first dose of brigatinib.
• patients with ECOG PS > 2	• The ALTA-1L trial included patients with ECOG PS of 2 or less. Most patients in the trial had ECOG PS of 0 or 1. The CGP noted that approximately a quarter to a third of the patients seen in clinical practice have worse performance status than patients included in the ALTA-1L trial (ECOG greater than 2). pERC agreed with the CGP that it would be reasonable to offer brigatinib to patients with ECOG PS of greater than 2 in patients whose ECOG PS may be related to the underlying disease or tumour symptoms.
• patients with symptomatic CNS metastases.	• The ALTA-1L trial limited eligibility to patients with asymptomatic CNS metastases as long as patients did not require an increasing dose of corticosteroids to control symptoms within 7 days before randomization. Exploratory subgroup analyses in the ALTA-1L trial suggested that brigatinib was associated with improvements in PFS compared to crizotinib in patients with and without intracranial CNS metastases at baseline. pERC agreed with the CGP that it would be reasonable to offer brigatinib to patients with and without brain metastases.
PAG is seeking advice on a time-limited need to cover patients who were receiving treatment with crizotinib or alectinib and	pERC agreed with the CGP that it would be reasonable to offer brigatinib on a time-limited basis to patients who have recently started crizotinib therapy because alectinib was not accessible

may be better candidates for treatment with brigatinib.	to them. However, if patients have been receiving crizotinib for a longer period of time and are doing well, switching these patients from crizotinib to brigatinib would not be indicated. The CGP noted that alectinib is currently funded in all provinces in Canada, except Prince Edward Island. pERC agreed with the CGP that there is insufficient evidence to ascertain the treatment effect of brigatinib in patients who have started treatment with alectinib. Furthermore, pERC agreed with the CGP that here is currently no robust evidence to ascertain which of the agents (i.e., brigatinib or alectinib) has superior efficacy. Therefore, pERC does not support offering brigatinib on a time-limited basis in patients who are currently receiving alectinib and have not progressed. However, pERC felt that it would be reasonable to offer brigatinib to patients who are unable to tolerate alectinib.
Implementation factors	
PAG is seeking clarity on treatment until "disease progression" and "unacceptable toxicity."	Treatment continued in the ALTA-1L trial until disease progression or intolerable toxicity occurred. Tumour response assessments were conducted every 8 weeks and assessed per RECIST v1.1 by the BIRC and the investigator until BIRC-assessed disease progression. After experiencing progressive disease, patients in the brigatinib group could continue the study treatment if they continued to experience clinical benefit in the opinion of the investigator. For patients who continued brigatinib beyond disease progression, tumour assessments continued to be performed every 8 weeks. In NSCLC with molecular aberrations and effective targeted drugs, Canadian clinical practice is to treat until lack of clinical benefit (progressive, symptomatic disease). pERC agreed with the CGP that the trial parameters in the ALTA-1L trial set for treatment discontinuation are reasonable and reflective of clinical practice.
Sequencing and priority of treatment	
What treatment options would be available to patients who progressed on brigatinib? What evidence is there to inform the sequencing of alectinib or other ALK TKIs after first-line brigatinib?	pERC was unable to make an informed recommendation on the optimal sequencing of available treatments following progression on treatment with brigatinib. pERC noted that it did not review evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of brigatinib and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
What treatment options would be available to patients who discontinued brigatinib in the case of toxicity?	In the absence of sufficient evidence to inform this situation pERC agreed with the CGP that intolerance to any ALK inhibitor in the first-line setting (crizotinib or alectinib) would be reasonable grounds for consideration of brigatinib and vice versa. It is recognized that the ALK inhibitors have differences in their toxicity profiles and patients may have better side effect profiles with an alternate to allow ongoing disease control.
If brigatinib is reimbursed, is there a preference for brigatinib or alectinib in the first-line setting? Under what circumstances would first-line brigatinib be preferred over first-line alectinib?	pERC agreed with the CGP that given the absence of a direct comparison, there is no robust evidence to ascertain which of the drugs (i.e., brigatinib or alectinib) has superior efficacy or a better safety profile. pERC and the CGP anticipated that some clinicians may prefer using alectinib as the trial evidence for alectinib has longer follow-up time (median follow-up time in the ALEX trial was 37.8 months) than the trial evidence for

	brigatinib (median follow-up time in the ALTA-1L trial was 24.9 months). In addition, Canadian clinicians are generally more experienced with alectinib than with brigatinib. Situations in which there would be preference to use alectinib may include patients who have baseline dyspnea or hypoxia (given the rare complication of an early onset pulmonary event), or poorly controlled hypertension. Alternatively, there may be a preference to use brigatinib if there are concerns about the development of weight gain, peripheral edema, myalgia, constipation, or blurry vision.

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